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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

OCTOBER, 1950

ORIGINAL ARTICLES

CLINICAL ORBITONOMETRY*

By J. H. Means, M.D.

AND

John B. Stanbury, M.D.

BOSTON, MASSACHUSETTS

(From the Thyroid Clinic of the Massachusetts General Hospital)

In the management of Graves' disease the type of course which the orbital lesion will take, whether a benign one or the so-called malignant, is of vital concern to doctor and patient. In planning the treatment, the doctor would like to know in advance what sort of behavior he may expect the eyes to exhibit. He would like to avoid therapeutic procedures such as thyroidectomy which may be likely to aggravate the ophthalmopathy. In this disease he is constantly confronted with the dilemma that what may benefit the thyrotoxicosis may injure the eyes, and vice versa.

Of course, what we really need to know are the etiology and the pathogenesis of the whole disease, and, in particular, that of its eye component. It is to be presumed that the eyeball is pushed out because of the orbital tissue swelling, but why does it swell? Various bits of evidence connect the ophthalmopathy with the thyrotropic hormone of the pituitary—for example, production of exophthalmos in animals by the administration of thyrotropin[1,2] or the elevation of thyrotropin level in the blood in human cases of malignant exophthalmos[3,4].

Another approach that may ultimately prove fruitful is the careful testing by quantitative methods of the effect of various agents and procedures in the ophthalmopathy in human cases.

Exophthalmometry has long been available and in a limited way is useful, but one would like to measure more directly the *vis a tergo* which propels the eyeball forward. A way of getting at this is to observe the effect of a *vis a fronte* by noting the extent of backward displacement that can be effected by a given pressure directed against the anterior aspect of the eyeball.

Von Graefe[7], as early as 1868, introduced testing of the resistance of the globe to backward displacement by palpation, and we have commonly employed it ourselves, but obviously such a method is crude and gives approximate information only. In 1910 Lan-

* Generously supported by grants from Parke Davis and Co., Detroit, Michigan, and the UNC gift of Harvard University.

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genhan[8] was the first to design an instrument actually to measure the repressibility of the eye into the orbit. It was, however, apparently rather unsatisfactory. An improved apparatus was described in 1941 by Georg[3] of the Eye Clinic in Berlin, under the title "Ein Neues Piezometer", from the Greek π ι ε ζ ω (piezo) to press. We were making some abortive attempts at the construction of such an instrument at the time Georg's paper first came to our attention. We made no real progress, however, because of difficulties as to the problem of how best to apply the instrument to the eyeball, and it was not until the spring of 1949 when we received from Copper of Leiden, Holland, a copy of his monograph[2], entitled "Clinical Orbitonometry" and containing a description of an improved and excellently simple instrument, that we were able to undertake systematic clinical measurements.

Copper's orbitonometer*, as he calls it, modeled closely after Georg's consists of 3 parts, a contact shell, a bridge and a dynamometer. The contact shell (Fig. 1., C) has a small plastic cup affixed to its convex side. This can easily and without discomfort to the patient be affixed to the novocainized anterior surface of the eyeball. The bridge (Fig. 1, B) which is slitted lengthwise is adjustable as to length. It is held in place by supports which fit the outer angles of the orbits and an elastic head band. The bridge also is equipped with an ad-

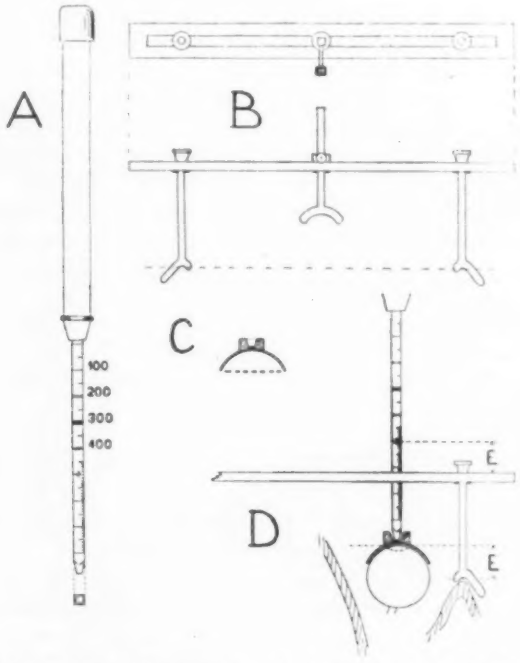

FIG. 1.—Diagram of the Copper orbitonometer. *A*, the plunger. *B*, the bridge. *C*, the contact shell. *D*, the mounting with shell on orbit, bridge in place, and plunger resting on the shell. *E* is the reading on the plunger which is equal to the protrusion of the eye. For description see text (after Copper). (Reproduced with the permission of the author and publisher[2])

* Obtainable from The Dixey Co., Ltd., 9 Cavendish Square, London, England.

justable nose piece. The dynamometer (Fig. 1, A) consists of a metal housing containing a spring and a plunger which acts against the latter. The plunger has 2 scales, an upper graduated in gm., which indicates the pressure applied against the spring, and a lower graduated in mm. The plunger is passed through the slit in the bridge and its foot rests in the cup of the contact shell. Readings are taken for distance on the mm. scale of the plunger against the bridge and for pressure on the gm. scale of the plunger against the margin of the orifice of the housing. Starting with zero pressure one reads the millimeter scale, then one applies pressure, taking readings of distance for each 100 gm. increment of pressure up to 400 gm. (Fig. 2).

In practice it has been difficult to fit the supports of the bridge into the outer angles of the orbit in such a fashion that reproducible zero readings are obtained. Uniformity has been secured by correcting the displacement values with Hertel exophthalmometric readings. It has also been necessary to calibrate the dynamometer from time to time.

The measurements require but a few moments and we have observed no untoward effects. If the patient complains of discomfort we discontinue the observation, but this has rarely happened. Copper reports that in 900 measurements 2 patients showed initial signs of faintness. He interpreted this as a bulbo-cardiac reflex. We have not encountered this result. We have refrained from making measurements in patients with any organic disease of the cornea, conjunctiva or globe. Also, on the advice of Dr. David Cogan, our ophthalmological colleague, patients with marked myopia have also been avoided, the fear being that retinal detachment might be occasioned. We have also avoided making measurements on patients with severe heart disease.

The results are plotted on a single graph of distance against pressure as

FIG. 2.—Method of taking a reading. Approximately 5 seconds is allowed at each tension before the displacement is noted.

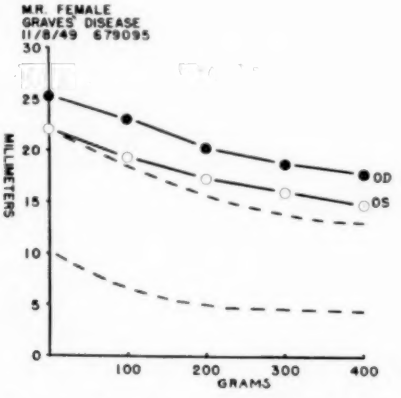

FIG. 3.—M. R., a patient with classic Graves' disease. Ordinate, protrusion of eye in millimeters. Abscissa, tension applied in gm. OD, right eye. OS, left eye. The dotted lines represent the 95 percentile limits obtained on 20 normal females.

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in Fig. 3. The patient of this graph, a young woman with moderately severe Graves' disease, had considerable proptosis, and lid retraction. There was excessive tearing and moderate periorbital edema. The right eye was slightly more prominent than the left. This difference is apparent from the figure. One can see at a glance the flattening of the curve and the slightly reduced displacement. In this figure is also shown the 95 percentile limits of 20 normal female subjects measured by Copper.

In following the course of a patient who may be developing changes in his eyes, one might wish to make measurements at frequent intervals. In this way he might find evidence of trends not at once evident from casual observations of the eyes. To be of value the instrument would have to give reproducible results. This reproducibility is illustrated in Fig. 4. This patient, who was also the subject for Fig. 3, underwent a trial of adrenocorticotrophin therapy for the Graves' disease. The values obtained daily with the orbitonometer seemed to be quite stable and reproducible, and were uninfluenced by the ACTH therapy, in spite of the fact that there was concomitant striking clinical improvement, fall in basal metabolic rate, and fall in the serum precipitable iodine.

To date we have made approximately 200 measurements on 53 patients. Some of them had no evidence of eye disease: the rest presented the various eye manifestations of Graves' disease. Unfortunately we have had a very limited opportunity to observe

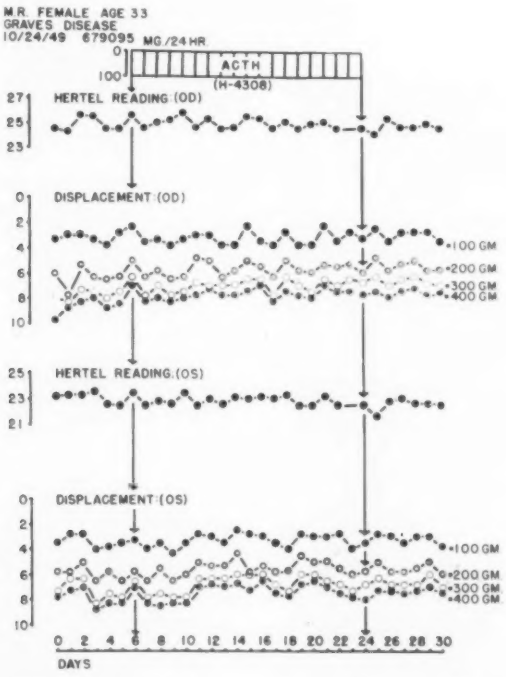

FIG. 4.—M. R., the same patient of Fig. 3. Diagram designed to show the stability of the instrument for day to day readings. The ordinates are in mm. except that of the adrenocorticotrophin which is in mg. per day. The abscissa is in days. The figures at the right are the successive increments of pressure applied to the globe by the plunger.

patients with malignant exophthalmos. Most of our data might be classified as background or control. The purpose in making this report is primarily to publicize a method which may prove to be useful in the examination of the patient with Graves' disease and in the interpretation of the ophthalmic component. It should also find a field of usefulness in the diagnosis of other orbital lesions such as tumors and aneurisms.

Georg[6] was chiefly concerned with the differential diagnosis of the exophthalmos of Graves' disease from that of orbital tumors, but our object is to distinguish between benign and malignant forms of the Graves' ophthalmopathy and between active and inactive processes. We are also interested in observing with the orbitonometer such changes as may occur when various forms of treatment are tried. We already have made limited observations during treatment with adrenocorticotrophin, iodide, propyl thiouracil and thyroid. Such new agents as may from time to time be suggested can also be tested.

Our data are insufficient to present any certain conclusions concerning the variations in the orbital resistance in various disease states. They suggest that orbitonometry in the ophthalmopathy of ordinary Graves' disease differs in no way from the normal state. However, when congestive phenomena are present, such as tearing, chemosis and vascular injection, the resistance is increased and the curve is flattened. Several patients with severe proptosis who are now free of the congestive phenomena described in their past histories have shown an increased backward displacement of the eyes. Thus it may be possible to follow the course and severity of the disease in a quantitative fashion. If it can be shown that an increased orbital resistance occurs before the congestive phenomena which are diagnostic of malignant exophthalmos, then one would have a means of predicting the course which the disease might take and of governing his therapy more wisely.

Summary. The need for a method for increasing the orbital resiliency has been met by an instrument devised by Dr. Copper of the University of Leiden, Holland. The instrument is simple to use. Reproducible data are quickly obtained without apparent risk or great discomfort to the patient.

Experience to date suggests that orbital resistance is increased in the active phase of the ophthalmopathic types of Graves' disease, diminished in the inactive phase of that disease, and little changed in ordinary Graves' disease. The instrument should prove of value in following the course of the eye lesion of Graves ophthalmopathy and may be helpful in the early differential diagnosis of the benign and malignant forms.

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PROPYLTHIOURACIL IN THYROTOXICOSIS; ALTERNATE CASES TREATED MEDICALLY AND SURGICALLY

By Nelson Taylor, M.D.

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and

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A wealth of literature has accumulated concerning the thiourea derivatives and their place in the treatment of hyperthyroidism since Astwood introduced these substances for clinical use[1,2]. The majority of workers in this field have decided that the antithyroid drugs find their greatest usefulness in the preparation of severely toxic and poor risk patients for operation, and that prolonged medical treatment is seldom justifiable[6,7,8,9]. However, Astwood[12] and others[4,5,11] have stated that these drugs should replace surgery almost completely in the management of the hyperthyroid states. These widely divergent views may be related to lack of adequate control in the studies that have been reported. Accordingly the present investigation was undertaken in an attempt to clarify this problem by the selection of alternate cases of diffuse goiter with hyperthyroidism for medical and surgical treatment.

Method of Study. All patients suspected of having hyperthyroidism are studied in the hospital and are evaluated by a combined medical surgical thyroid group. After the diagnosis of hyperthyroidism has been established and treatment instituted, the patients are followed in the out-patient endocrine clinic, and all pertinent data are tabulated on charts prepared for that purpose.

Measurements of the degree of exophthalmos are made with the Hurtel exophthalmometer, in consultation with the department of ophthalmology.

The patients with diffuse goiter and hyperthyroidism are assigned alternately to medical and surgical groups at the time that the diagnosis is established by the thyroid group. All patients with nodular goiter are advised to have thyroidectomy unless specific contraindications exist.

Propylthiouracil* is the antithyroid drug which has been used in all cases. At the beginning of this study, it was given in doses of 100 mg. every 8 hours if the BMR was consistently above plus 50%, and in doses of 50 mg. every 8 hours if below plus 50%. This plan recently has been altered so that now the larger dose is employed initially in all cases. In addition, supplemental vitamins and a high caloric, high protein diet are prescribed. Uncomplicated cases are studied for about 2 weeks in the hospital; those with complications remain in the hospital as long as is necessary and are discharged to be followed in the clinic when conditions warrant. Leukocyte counts are taken regularly on all patients during treatment. They were done every other day early in the study; the interval was then gradually increased to weekly, and now uncomplicated cases are seen but once each month at which time the counts are obtained.

The medical cases are treated by decreasing and, if possible, eliminating the propylthiouracil when the BMR reaches normal. The surgical cases are treated with propylthiouracil until the BMR approaches normal at which time iodine is given for 3 weeks to involute the gland and decrease its vascularity. Subtotal thyroidectomy then is per-

* During the first 2 years of this study the Lederle Company supplied all of the propylthiouracil (Probacil) (R) and is now continuing to provide a portion of that used.

TABLE 1.—PHYSICAL FINDINGS.

	No. of Patients		*No. of Patients*
General Nutrition		Cardiovascular	
Obese	6	Cardiac enlargement	28
Average	15	Auricular fibrillation	8
Underweight	31	Systolic hypertension	20
		Diastolic hypertension	6
Hyperstimulation	43	Pulse pressure greater than 50	46
Exophthalmos	32*	Pulmonary congestion	6
Enlarged Thyroid Gland	51	Hepatomegaly	17
Diffuse 41**			
Nodular 11		Fine Tremor	47

* Exophthalmos occurred only in cases of diffuse goiter with hyperthyroidism.

** The one case in which the gland was not palpable is considered to be a diffuse goiter.

formed. Propylthiouracil is withheld during the week preceding operation.

Clinical Findings and Results of Treatment. The total number of patients in this 2-year study is 90. Diagnostic data are adequate on 52 patients; of these, 37 have been followed and studied in detail for a sufficiently long period to permit conclusions.

The classical symptoms of thyrotoxicosis were found quite uniformly, though the history of weight loss associated with polyphagia was the cardinal symptom. The majority of the patients had other diseases, many of them serious. Indeed, only 9 of the 52 patients were admitted with uncomplicated thyrotoxicosis. Thirty-six had associated diseases, and 31 had thyrotoxic heart disease.

The physical findings associated with hyperthyroidism in the 52 cases are given in Table 1. Exophthalmos was present and confirmed by exophthalmometry in 32 patients, all with diffuse goiter. An enlarged thyroid gland was palpable in 51 of the 52 patients but could not be felt in one patient who had a thick short neck. The complications of thyrotoxicosis that occurred in this series are shown in Table 2. Thyrotoxic heart disease was present in 31 of the 52 patients. In all of these cases the prolonged use of propylthiouracil resulted in great improvement in cardiac status so that operation was done, when indicated, without mortality.

TABLE 2.—COMPLICATIONS OF THYROTOXICOSIS IN 52 PATIENTS.

Complication	*No. of Patients*
Thyrotoxic heart disease	31
Increasing exophthalmos	8
Thyroid crisis	3
Severe vitamin deficiency	2
Severe anxiety state	1

Three patients were admitted to the hospital in impending or actual thyroid crisis. They were given sodium iodide intravenously and intensive supportive therapy; all 3 survived. No postoperative crises occurred.

As mentioned earlier, cases of diffuse toxic goiter were alternately assigned to medical and surgical groups at the time the diagnosis was established. We would prefer to have operated upon all the nodular cases because of the possibility of malignancy, but the risk of operation was considered too great in one of these patients even after

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prolonged medical management, and several others refused operation. Thus the 52 cases of hyperthyroidism are conveniently arranged into 4 groups: surgical diffuse, medical diffuse, surgical nodular, and medical nodular. The distribution of the cases into these groups is given in Table 3, which also shows that 15 patients were lost, 9 of whom were in the medical diffuse group. It will be noted also that 3 patients had to be transferred from the medical to the surgical diffuse group. This was because of increasing exophthalmos, increasing size of the goiter, and in one case poorly controlled diabetes. One patient was transferred from the surgical to the medical diffuse group because he refused operation. Thus the number of satisfactorily followed cases of Graves' disease treated medically is 12 out of 21 (57%), and of those treated surgically, 16 out of 20 (80%).

The 4 patients in the medical nodular group deserve some comment. All had serious associated heart disease (Table 3). One was admitted to the hospital semicomatose following a cerebral vascular accident. The second was uncooperative, continued treatment only sporadically and was finally readmitted to the hospital with massive rectal hemorrhage from which she

TABLE 3.—ARRANGEMENT OF 52 CASES OF HYPERTHYROIDISM INTO GROUPS.

	Diffuse Surgical	*Diffuse Medical*	*Nodular Surgical*	*Nodular Medical*
Total cases	18	23	7	4
Adjusted total*	20	21	7	4
Thyrotoxic heart disease	10	12	5	4
Cases lost	4	9	1	1
Cases followed	16	12	6	3

* 1 patient was transferred from the surgical diffuse to medical diffuse group, 3 from the medical diffuse to surgical diffuse group.

TABLE 4.—RESULT OF TREATMENT IN 52 CASES OF HYPERTHYROIDISM.

	Diffuse Surgical	*Diffuse Medical*	*Nodular Surgical*	*Nodular Medical*
Total no. of patients	20	21	7	4
No. of patients followed	16	12	6	3
Average initial BMR	56	55	60	59
Average dose propylthiouracil to normal BMR or operation (gm.)	37.8	29.8*	85.6	77.6
Average duration of treatment with propylthiouracil to normal BMR or operation (days)	169	118	368	273
Sustained remission without further therapy	13	3	6**	0
Hypothyroidism	3	0	0	0
Still receiving propylthiouracil	0	9	0	2***

* 7 cases; in the others the BMR is still elevated.

** 1 patient died of carcinoma of colon 15 months after thyroidectomy.

*** 1 patient died of unexplained gastrointestinal hemorrhage.

died; the third and fourth patients refused operation.

Table 4 shows that the medically and surgically treated cases are suitable for comparison inasmuch as the average initial BMR fell between plus 55 and plus 60 for all 4 groups. Table 4 also gives the duration of treatment and the results obtained. The average period of treatment required to bring the BMR to normal was almost a year in the cases with nodular goiter and about 5 months in the cases with diffuse goiter. There was only slight correlation between the initial BMR and the total dose of propylthiouracil (or duration of treatment) required to bring the patients to euthyroid status. This is illustrated in Fig. 1. All the surgical diffuse cases survived operation and are well, but 3 must take desiccated thyroid to control hypothyroidism. Only 3 of the medically treated cases remain euthyroid after cessation of treatment; the others still require the continued administration of propylthiouracil for control of their hyperthyroidism.

Undesirable effects of propylthiouracil included: toxicity, changes in exophthalmos, and increasing enlargement of the thyroid gland.

Toxicity. The single case of agranulocytosis included in this series had been treated elsewhere. She had received thiouracil 0.6 gm. daily for 2 weeks and 0.4 gm. daily for 9 days when her total leukocyte count dropped to 1600 with no granulocytes. Penicillin, liver extract and folic acid were employed with satisfactory response. The hyperthyroidism was apparently in remission, but one month later there was a relapse which failed to respond to Lugol's solution employed for 12 days. Thereafter propylthiouracil, 150 mg. daily, was given for 23 days at which time a severe ulcerative pharyngitis appeared, and 2 days later the patient was admitted to Receiving Hospital. The leukocyte count was 3100 with 1% granulocytes. Penicillin therapy was begun, but two days later the white cell count was 1700 with 1% granulocytes. However, the count began to rise on the following day and pro-

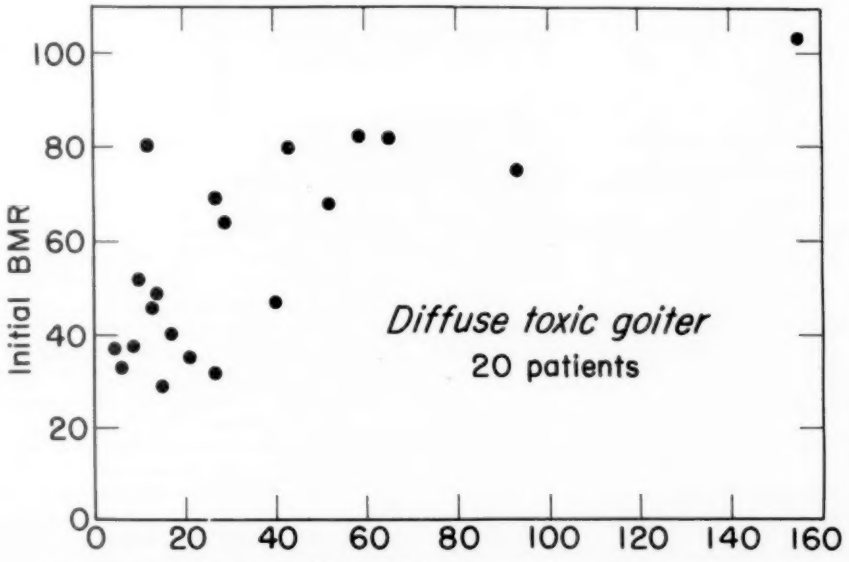

FIG. 1.—Total dose of propylthiouracil (gm.) required to bring BMR to normal.

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gressively increased to normal during the next few days. The patient thereafter was prepared satisfactorily with iodides, and thyroidectomy was accomplished without incident.

One patient's white count fell to 2300 total with 31% granulocytes during treatment. The propylthiouracil was stopped, but was started again 2 days later and continued with no ill effect.

Sialadenitis involving all the salivary glands appeared in 2 patients, 6 months after each had discontinued treatment with propylthiouracil. It is assumed that these were mere coincidences. Fortunately neither patient was very ill and both recovered spontaneously within 2 to 3 weeks.

Changes in Exophthalmos. The results of this part of the study are shown in Fig. 2. Twenty-two patients were followed wth frequent exophthalmometer readings. Although the average increase in exophthalmos during propylthiouracil therapy was only 2 mm., the marked increase in 5 of the cases is striking. These figures may be compared with the changes which occurred in 9 of these same 22 cases adequately studied following thyroidectomy. The trend toward a decrease is shown in the chart. Since these observations differ from the experience of others, several illustrative case reports are presented.

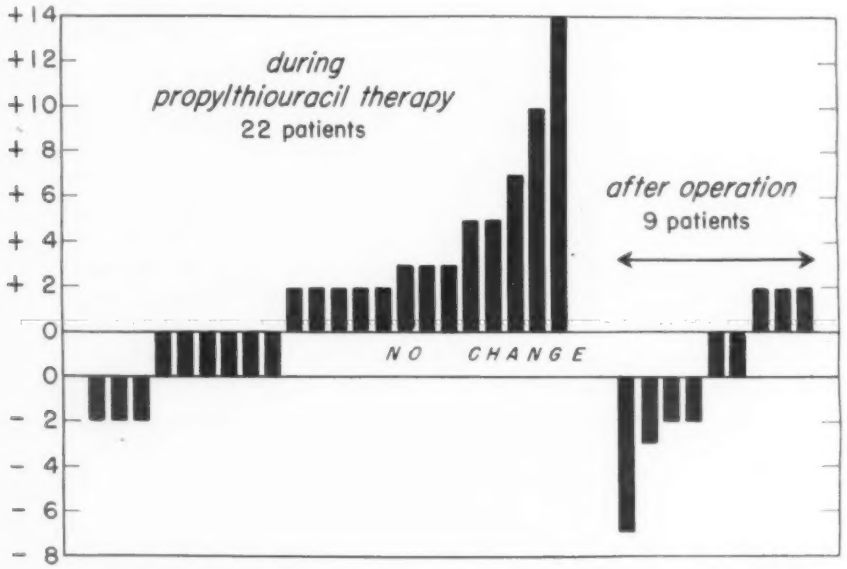

FIG. 2—Changes in exophthalmos. Each bar represents 1 patient.

Case Reports. CASE 1. H. S., a 52 year old colored male, was discovered to have diffuse goiter with hyperthyroidism in October, 1947, while under treatment for urethral stricture. He was assigned to the medical group and given propylthiouracil, 100 mg. every 8 hours. His course is graphically depicted in Fig. 3. A slow improvement in thyrotoxic symptoms and a gradual fall in BMR occurred during the next 11 months. However, exophthalmos, which had not been present before treatment was started, became noticeable 5 months after propylthiouracil was begun and was progressive (Fig. 4). It was therefore decided that treatment of the eyes must take precedence over the hyperthyroidism. Although thyroidectomy was considered, we had had little experience with progressive exophthalmos at the time and feared that the operation

might result in further increase of exophthalmos with loss of vision. Desiccated thyroid was given with no effect and the patient's vision began to be impaired. Therefore a bilateral Naffziger orbital decompression was performed. Following the operation, iodine, testosterone and pituitary irradiation were used and some improvement in vision occurred, but when the patient was last seen in February, 1949, he was still suffering from moderately severe hyperthyroidism, exophthalmos was marked, and vision was still impaired.

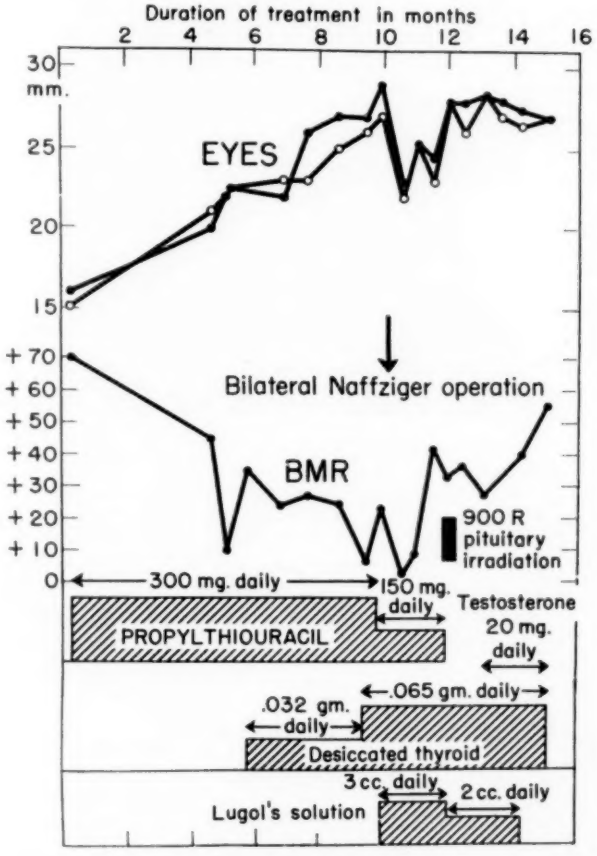

FIG. 3.—Course of Case 1.

CASE 2. J. M., a 20 year old white male, who had had diabetes mellitus since childhood, was admitted with diffuse goiter and hyperthyroidism of 3 months' duration. He was assigned to the medical group and was given 100 mg. of propylthiouracil every 8 hours. The course is depicted in Fig. 3. During the first 12 months of treatment the BMR fell gradually from an initial level of plus 70 to plus 20, but progressive exophthalmos developed. The right eye measurement was 18 mm. before propylthiouracil and increased to 23 mm. after a 12 month course; corresponding figures for the left eye were 16 mm. before and 21½ mm. after. The diabetes was at first controlled on 120 units of insulin daily, but the requirement steadily increased so that 12 months later 154 units daily were inadequate. The thyroid gland also became larger with an increase in neck circumference of 4 cm. He was transferred to the surgical group and subtotal thyroidectomy performed after preparation with iodides. Following operation a temporary increase in exophthalmos occurred, but then a significant decrease was noted,

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FIG. 4.—Case 1. Progressive exophthalmos.

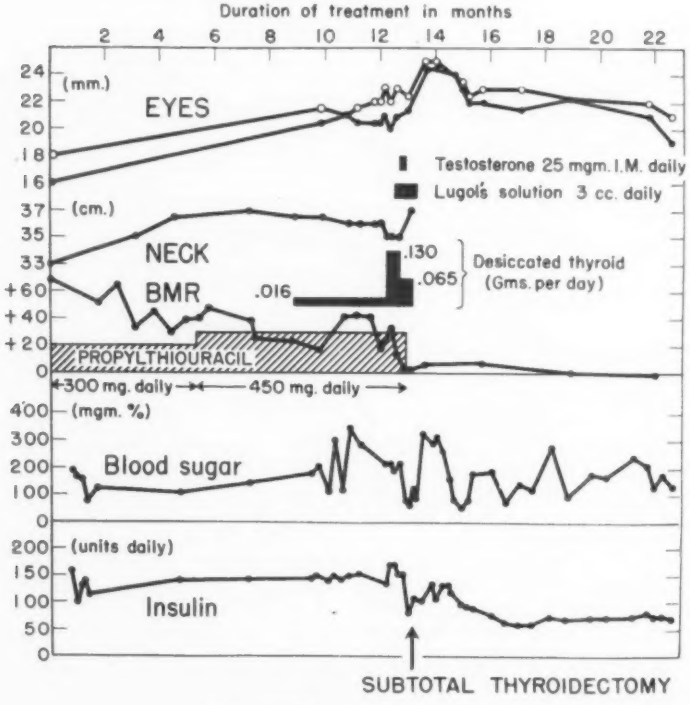

FIG. 5.—Course of Case 2.

and 6 months later the measurements were as follows: O.D. 21 mm., O.S. 19 mm. During this period the insulin requirement had decreased to 70 units per day and the diabetes was well controlled.

CASE 3. J. B., a 43 year old colored male with diffuse goiter and hyperthyroidism, assigned to the medical group, was treated with 100 mg. of propylthiouracil every 8 hours. The BMR fell from plus 64 to plus 9 in 3 months, but he developed progressive exophthalmos, the right eye increasing from 22 to 27.5 mm. and the left eye from 22 to 27 mm. Upon recommendation of the ophthalmological consultant, the patient was transferred to the surgical group and subtotal thyroidectomy performed. Two months after operation the exophthalmos had receded to O.D. 26 and O.S. 24.

CASE 4. F. G., a 30 year old colored female with Graves' disease, was treated medically with 100 mg. of propylthiouracil every 8 hours. The BMR fell from plus 75 to plus 18 over a 14 month period, but marked enlargement of the thyroid gland occurred. The neck circumference increased 4.5 cm. She also developed increasing exophthalmos which progressed from O.D. 20 and O.S. 20 mm., to O.D. 23 and O.S. 23.5 mm. She was transferred to the surgical group and subtotal thyroidectomy was performed. The exophthalmos has remained static at O.D. 23 and O.S. 22.5 mm., but the patient has no symptoms referable to the eyes and remains well 8 months after operation.

CASE 1 did not have thyroidectomy. He developed severe exophthalmos which persists in spite of orbital decompression. Cases 2, 3 and 4 also developed progressive exophthalmos while on propylthiouracil. Cases 2 and 3 showed actual decrease by measurement after thyroidectomy, and in Case 4 the progression of exophthalmos stopped. Cases 2 and 4 also illustrate the goitrogenic effect of propylthiouracil with resulting increase in size of the thyroid gland. In addition there was the disappointing failure to ameliorate diabetes mellitus in Case 2.

Deaths. During this study there were no deaths due to thyroidectomy or to propylthiouracil therapy, but 2 deaths did occur, both in patients with toxic nodular goiter. One of these, already mentioned, was uncooperative and died of massive rectal hemorrhage several months after unauthorized cessation of treatment. The other, a 65 year old white female, died of carcinoma of the colon about 15 months following thyroidectomy.

Pregnancy. Two pregnant patients with hyperthyroidism have been observed. The first was on treatment with propylthiouracil and was gradually coming under control when it was found that she was 2 months pregnant. The drug was discontinued, preoperative iodine was given and thyroidectomy performed. The patient later was delivered of a normal infant. The second patient was first seen in the 25th week of pregnancy with moderately severe thyrotoxicosis. Iodides and Roentgen therapy were used but without demonstrable effect. In the thirty-second week she went into labor spontaneously and delivered a premature infant which appeared normal and is exhibiting normal development. No propylthiouracil was employed.

Discussion. There have been a large number and variety of associated diseases in this study; only 9 of the 52 patients had uncomplicated thyrotoxicosis. Most of the patients were severely toxic inasmuch as two-thirds of those studied in detail had pretreatment BMRs repeatedly found to be over plus 50%. There is no adequate explanation for the long periods of treatment required other than that of severe toxicity. However, there were some instances of mild thyrotoxicosis which also necessitated prolonged therapy to bring the BMR to normal level. The cooperation of patients who continued treatment long enough to be reported herein has been exceptionally good. Each individual was given only enough propylthiouracil to last until the next appointment and returned the con-

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tainer to demonstrate that the medication had been taken regularly. However, all patients were indigents with home environments which might easily include considerable psychic trauma, a factor which could interfere with response to therapy.

Although one case with toxic nodular goiter was not operated upon because the risk was considered too great, no such exceptions were made in the diffuse cases. The complications were as frequent and as severe in the surgical as in the medical cases (Table 3), yet no deaths occurred in the surgically treated cases. This absence of operative mortality indicates the value of propylthiouracil in preparing the poor risk patient for operation.

Comparison of the medically and surgically treated cases of diffuse toxic goiter is difficult and the present series is too small to justify any definite conclusions. However, the surgically treated cases had excellent results and the hypothyroidism which occurred in 3 patients is easily controlled by the administration of desiccated thyroid. On the other hand, almost half of the medical group failed to continue treatment and were lost, 3 others had to be transferred to the surgical group, and only 3 patients have had sustained remissions after propylthiouracil was discontinued. Thus from the practical point of view, we prefer to treat diffuse toxic goiter by subtotal thyroidectomy. Mild cases without complications may be prepared with iodine and operated upon. The more severely toxic and poor risk patients can be converted to satisfactory candidates for operation of prolonged treatment with propylthiouracil. This point has been repeatedly stressed by many workers in this field, particularly Lahey[8].

Certain patients with small goiters may be satisfactorily controlled by propylthiouracil, but if the goiter increases in size or associated diseases become aggravated, operation is indicated.

Toxic effects of propylthiouracil have not constituted a major problem in this small series. The one case of agranulocytosis responded well to penicillin and supportive therapy.

Much more important, in our experience, is the tendency for exophthalmos to become progressive during propylthiouracil therapy. The first of these cases that we observed (Case 1) had no exophthalmos when first seen, but developed rapidly increasing protrusion of the eyes while on propylthiouracil. Medical treatment was used throughout and, in addition, orbital decompression, but marked exophthalmos was still present when he was last seen. The poor result in this case led us to believe that some other form of treatment ought to be substituted for propylthiouracil if progressive exophthalmos should be observed in any other cases under treatment. Accordingly subtotal thyroidectomy was performed in Cases 2, 3 and 4 when increasing exophthalmos became evident. An excellent result was obtained in each case with either cessation of the progression or actual regression of the exophthalmos. The average finding in this series of an increase in exophthalmos during propylthiouracil treatment, and either no further increase or an actual decrease after thyroidectomy, supports the idea that this procedure is a rational one.

We are aware of the possibility that in the occasional case of Graves' disease, thyroidectomy may produce further progression of exophthalmos. Our experience, however, does not coincide with the findings of those who have reported a more definite and consistent increase in exophthalmos after thyroidectomy than during treatment with the antithyroid drugs[3].

Regardless of how our results fit the generally accepted theory of anterior pituitary control of exophthalmos, from the practical aspect we believe it important to observe patients closely for progressive exophthalmos. When increasing protrusion of the eyes becomes apparent, thyroidectomy is planned as soon as possible. It is recognized that a total of 52 patients observed over a 2-year period is not a sufficiently large enough series to justify sweeping conclusions, but the postoperative regression of exophthalmos in those patients with the more marked progression on propylthiouracil warrants continuation of this plan of treatment until further experience has been obtained.

Management of the pregnant patient with hyperthyroidism is difficult. Because of both experimental and clinical evidence[10] that propylthiouracil given to the mother affects the fetal thyroid and might result in cretinism or myxedema in the child, we prefer not to give the drug after the 14th week of pregnancy at which time the fetal thyroid becomes functional. The 2 pregnant patients in this series were managed successfully without the use of antithyroid drugs.

Since this series is small and since some of our observations are at variance with those reported by others, the study is continuing with alternation of cases of diffuse toxic goiter into medical and surgical groups.

Summary. 1. Ninety patients with hyperthyroidism have been observed on the wards and in the out-patient department of a charity hospital during a 2-year period. Data are adequate on 52 patients and 37 have been studied in detail.

2. The level of toxicity was high with the BMR above plus 50% in more than two-thirds of the group. Complications of thyrotoxicosis or associated diseases occurred in 43 of the 52 patients.

3. Alternate cases of diffuse toxic goiter were treated medically and by thyroidectomy.

4. Prolonged periods of propylthiouracil treatment were required in the majority of cases, possibly due to the large number of associated diseases, to the large number of complications, or to the high level of toxicity. Many of the medically treated patients were lost and only 3 of the remainder have normal BMRs without continuing treatment. Those patients treated surgically showed no mortality and the satisfactory results obtained are thought due to the conversion of the severely toxic and poor risk patients to mildly toxic and good risk patients by prolonged preparatory treatment with propylthiouracil.

5. Agranulocytosis occurred in one patient treated with antithyroid drugs elsewhere. Toxic manifestations from propylthiouracil did not otherwise constitute a problem.

6. A significant increase in exophthalmos occurred in 8 of 52 patients receiving propylthiouracil. There was no significant progression of exophthalmos in any case postoperatively, and definite regression occurred following thyroidectomy in 4 cases.

Conclusion. On the basis of our observations in this small controlled series of cases of hyperthyroidism, we are inclined to favor the continued use of subtotal thyroidectomy as the standard treatment for diffuse goiter with hyperthyroidism. Certainly until further experience has been gained, we intend to advise operation upon all patients who are being given antithyroid drugs and show any tendency toward progressive exophthalmos.

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OBSERVATIONS ON THE PROLONGED MEDICAL MANAGEMENT OF TOXIC DIFFUSE GOITER WITH THIOURACIL AND PROPYLTHIOURACIL

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The use of thiourea derivatives in the treatment of thyrotoxicosis has now had about 6 years of clinical trial. Although numerous reports of the results obtained with these compounds have been published, long-term studies have still been relatively few. The need for additional follow-up reports has been stressed by those interested in the evaluation of the ultimate usefulness of these compounds in the permanent control of thyrotoxicosis[7,18,23].

The present report is based on 70 cases of toxic diffuse goiter observed for the past 5 years. The majority of these were selected for prolonged medical treatment for one of the following reasons: a) thyroidectomy was refused, b) the presence of medical complications increased the surgical risk, c) thyroid resection had been performed and further surgery was deemed inadvisable or d) mild hyperthyroidism was present. Nodular goiters were not treated medically since it has been the policy of this clinic[17] to advocate removal of all adenomatous glands, especially the solitary nodule. This report deals briefly with the incidence and duration of remissions, with the alterations in the degree of exophthalmos and with changes in the size of the thyroid gland. It also includes observations regarding the use of pyridoxine hydrochloride as an adjuvant in the therapy when granulocytopenia supervenes.

An adequate course of treatment was considered to be at least 1 year of therapy, using an initial dose sufficient to bring the basal metabolic rate (BMR) down to the normal range, preferably to a minus level. Thereafter, the dose was reduced to the minimal amount which would maintain the patient at that level. The early cases were treated with thiouracil, the usual initial dose being 600 mg. daily, reduced to 300 mg. daily when the BMR reached the normal range, and then further reduced until the minimum maintenance dose was obtained. This latter dose was usually 100 mg. per day; in some patients 50 mg. per day proved adequate. When Astwood[1,2] reported, after testing more than a score of related compounds, that 6-propyl-2-thiouracil seemed to have advantages over the others, namely, greater potency and less toxicity, propylthiouracil was substituted for thiouracil early in 1946. This compound has been used exclusively since then. The average initial dose was 300 mg. per day (200 mg. in the milder cases) and again this was reduced to half the orig-

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inal dose when a normal BMR had been attained. Further reduction was often necessary until the maintenance dose was determined. This varied between 50 and 100 mg. per day. Occasionally, a patient could be maintained satisfactorily on 25 mg. per day.

It was felt that a significant remission after discontinuing the drug should extend for at least 6 months (preferably more than 1 year). This was based on the present observations and those of others[6,8,14,27,28] since relapses usually occur within 6 months after stopping the drug (the majority within 3 months). Furthermore, thyroid surgeons consider a year of freedom from return of symptoms as the criterion for a satisfactory post-operative remission (less than 12 months being considered a surgical failure[16]). It would seem logical to apply this yardstick to remissions in medical treatment.

Remission and Relapse. Forty-seven patients received a course of adequate therapy as previously described; 8 of these failed to return to the clinic for completion of treatment. Of 39 patients who had adequate treatment and follow-up examinations, 25 (64%) have had remissions for over 1 year and 30 (77%) for over 6 months (Table 1). Nine patients developed recurrence of the signs and symptoms of hyperthyroidism after cessation of the drug. One of these showed a relapse 10 months after completion of treatment. Of the remainder, 3 showed a recurrence in 1 month, 1 in 2 months, 2 in three months and 2 in 4 months. These observations suggest that following an adequate course of therapy, if a remission persists for 6 months, the probability of relapse is small; if the remission lasts for more than a year, the probability of recurrence is remote.*

TABLE 1.—REMISSIONS AND RELAPSES IN 47 PATIENTS WITH TOXIC DIFFUSE GOITER TREATED FOR 1 YEAR WITH THIOURACIL OR PROPYLTHIOURACIL

Response	*Duration*	*No. of Cases*	*Total*
1. Remissions			30
	over 4 yrs.	2	
	3–4 yrs.	3	
	2–3 yrs.	7	
	1–2 yrs.	13	
	6–12 mos.	5	
2. Relapses			9
	after 10 mos.	1	
	4–10 mos.	2	
	3–4 mos.	2	
	2–3 mos.	1	
	1–2 mos.	3	
3. Inadequate follow-up			8

* This statement requires some further explanation. The pathogenesis of toxic diffuse goiter is not known. In many cases, however, a history of a strong psychic insult may be obtained which had occurred days or weeks prior to the onset of symptoms. On the assumption that a remission has lasted for more than 1 year, it is conceivable that another powerful psychic stimulus may result in a recurrence of hyperthyroidism years later. In the present series, 1 such instance was noted. This patient was treated for toxic diffuse goiter with thiouracil for approximately 1 year. Thereafter, the patient was symptom-free and the BMR remained within normal limits for 3 years. Then her husband died suddenly and several weeks after this episode, she noted recurrence of tremors, sweats, and weight loss. A BMR confirmed the diagnosis of recurrent hyperthyroidism.

The sex incidence of the patients in whom thyrotoxicosis recurred after the thiourea derivatives were discontinued is worthy of note. Of the 39 patients who had adequate treatment, 5 were males; 4 of these relapsed when the drug was discontinued. Of the 34 female patients, only 5 developed recurrence after cessation of the antithyroid compound. A similar experience has been reported by other observers[4,5,6,28].

Other reports dealing with the incidence of remissions and relapses in patients with thyrotoxicosis treated with thiourea derivatives for a prolonged period of time do not indicate quite as high a percentage of lasting remissions as reported in this series[6,12,14,23,27,28]. Thus, Williams *et al.*[28] found remissions to persist in 46% of their patients while Frisk[14] noted remissions for longer than 6 months in 64% of his cases. Starr *et al.*[24] recently reported results which are at considerable variance with those of many observers. They found that in 7 of 28 patients, hyperthyroidism was not controlled by propylthiouracil and that a relapse occurred in nearly every case in which the drug was discontinued. Analysis of their report indicates that at least in some of the cases studied by Starr and his co-workers, an adequate course of treatment was not given; the duration of treatment was too short, the dose of propylthiouracil too small, or both. These authors quote a personal communication from Astwood[3] who found that 85% of his patients had lasting remissions after discontinuing propylthiouracil. The high remission rate in the present series is believed to be due to adequate dosage (sufficient to keep the BMR in the minus range) for a prolonged period of time (1 year).

Beierwaltes and Sturgis[9] recently reported their observations in 44 patients with thyrotoxicosis treated with propylthiouracil and small doses of iodine for an average of 10.6 months. Of these, 34 (77%), had remissions lasting from 3 to 36 months after discontinuing the drugs. It is of interest to note the close agreement of the findings in the above report and those of the present study wherein propylthiouracil was used without the simultaneous administration of iodine.

Failures. In 15 cases, an adequate course of therapy could not be completed. Nine cases developed toxic manifestations severe enough to force withdrawal of the drug. One of these developed marked granulocytopenia (granulocytes 25%) while on thiouracil therapy, and the drug was discontinued. For 6 months, this patient was treated with iodine and sedation. She was then placed on propylthiouracil and soon developed granulocytopenia as pronounced as when on thiouracil. This was the only patient in the series who developed a depression of granulocytes from propylthiouracil severe enough to force cessation of the drug. Another patient on propylthiouracil developed marked muscle weakness and the drug had to be withdrawn. The types and incidence of toxic manifestations are shown in Table 2. Of 37 patients receiving thiouracil, 7 had toxic reactions requiring withdrawal of the drug; of 46 on propylthiouracil, only 2 had toxic manifestations of a similar degree.

Failure to complete the course of treatment in 6 instances was due to the unreliability of the patient. Either because of fear, lack of understanding or irregularity in clinic attendance, these patients failed to take the medication regularly or in proper dosage; they were transferred to surgery. It is worthwhile to evaluate the personality and intelligence of the patient and his willingness to cooperate in a long

TABLE 2.—REASONS FOR FAILURE TO COMPLETE ADEQUATE COURSE OF THERAPY

1. Toxic manifestations	
A. *Thiouracil*	
1. Granulocytopenia	3
2. Muscle weakness	1
3. Skin rash	1
4. Arthropathy	1
5. Hepatitis	1
B. *Propylthiouracil*	
1. Granulocytopenia	1
2. Muscle weakness	1
2. Unreliability of patient	6

range program of this type before instituting prolonged medical therapy.

Exophthalmos. Observations on the effect of thiourea derivatives on thyrotoxic exophthalmos have been reported by several workers. The conclusions, however, have been at considerable variance. In some series, no improvement[26] or even a slight tendency to an increase in the proptosis[4,5,23] has been noted. In another study, no progression of the exophthalmos was observed[12,14]; some improvement occurred in a few[12]. Others have reported decrease in the exophthalmos in 45% of cases[19] or even better[21].

Eighteen patients with exophthalmos in this series were carefully observed. In the more severe cases, in which it was difficult to determine the changes by inspection, measurements were made by exophthalmometer*. In some cases, the improvement was so apparent to the clinicians and to the patient that measurements were not used. In no instance did the protrusion become obviously worse during or after medical treatment. Nine cases showed regression of the exophthalmos, partial or complete; 7 remained unchanged. In 2 patients, there was no change during thiouracil therapy, but the exophthalmos progressed after thyroidectomy. In 1 of these, during the entire course of therapy the exophthalmos remained unchanged. Four months after stopping the drug, the patient returned in relapse but without alteration in the degree of exophthalmos. Thyroidectomy was then performed, but because of inadequate surgery, the hyperthyroidism persisted post operatively. The exophthalmos became more pronounced soon after thyroid resection. The patient was given propylthiouracil in order to control the persistent hyperthyroidism but this failed to inhibit the progression of the exophthalmos.

Size of the Thyroid Gland. Apparently, satisfactory clinical responses to thiouracil and allied compounds may be attained without increase in the size of the thyroid gland[4,26]. Several workers have reported a tendency for the goiter to decrease in size or even to disappear[20,22].

In this series, observations on the

* The extent of improvement in exophthalmos that may be obtained in patients with thyrotoxicosis treated with thiourea derivatives is exemplified by the following studies in a 43 year old female patient: with the exophthalmometer always set at 105 mm., the initial readings for O.D. and O.S. were 22 mm. and 20.5 mm., respectively; after 3 months of propylthiouracil therapy, the readings were 21.5 mm. and 19 mm.; after 11 months, the readings were 20.5 mm. and 18.5 mm.; after completion of treatment (1 year) the readings were 20 mm. and 19 mm., respectively.

size of the thyroid gland were made before, during and after therapy in 27 cases. A gland was regarded as diminished in size only if more than one clinician and the patient agreed that it was smaller. In 13 patients, the gland decreased in size, in 12 it remained unchanged, and in 2 the goiter increased in the size. In neither of the latter 2 cases was the increase in size of the gland of a sufficient degree to cause pressure symptoms.

Patients Still Under Treatment. Seventeen patients are under treatment with propylthiouracil at the present time; 5 have not yet completed their full year of therapy. Each has shown the usual beneficial response to the drug. Twelve patients have been under treatment for more than a year; 7 are in the second year of treatment with these anti-thyroid compounds, 4 in the third year, and 1 in the fourth year. It was found necessary, and at times desirable, to continue the drug for periods longer than 1 year because: a) relapse had occurred after cessation of the drug and thyroidectomy was either refused, inadvisable or hazardous (4 cases); or b) persistence of complicating disorders such as hypertension, heart disease and diabetes mellitus of a severe degree prompted continuation of the anti-thyroid compound without interruption (8 cases). Throughout the prolonged therapy, the hyperthyroidism has been satisfactorily controlled in each of the 12 patients. No undesirable side-effects have been noted nor has any resistance to the drug resulted.

Pyridoxine Hydrochloride in Granulocytopenia. Granulocytopenia was a serious complication in several patients receiving thiouracil; rarely was severe granulocytopenia observed when propylthiouracil was administered. Based on the observations of Wilter, Schiro and Spies[25] and Goldman and Malvados[15], Cantor and Scott[10] treated 3 patients with agranulocytic angina with pyridoxine hydrochloride administered intravenously. In 1 patient in whom the agranulocytosis was induced by thiouracil, recovery followed the intravenous administration of pyridoxine. It has been postulated that pyridoxine is a maturation factor involved in the development of the neutrophil[11]. Fishberg and Vorzimer[13] suggested the use of prophylactic doses of pyridoxine by mouth daily in order to prevent leukopenia induced by these compounds.

Twenty-four patients who developed granulocytopenia in this series were given pyridoxine at various intervals. In patients receiving thiouracil, blood counts were usually made weekly. When propylthiouracil was administered, white blood cell and differential counts were determined every 2 weeks and especially when the initial larger doses were prescribed. Whenever the total white blood cell count and, or, the leukocyte count decreased sufficiently to indicate a significant toxic depression of the bone marrow (granulocytes less than 40%), pyridoxine by mouth was prescribed without altering the dose of the anti-thyroid drug. The amount of pyridoxine ordered varied with the degree of white cell depression and the dose of the anti-thyroid drug. Usually, 60 mg. daily in 3 or 4 divided doses was ingested. If no appreciable response in the blood count was noted after 1 week, the dose of pyridoxine was increased to 150 mg. and in one case to 225 mg. daily.

It is admittedly difficult to evaluate leukocyte and granulocyte response as cell counts may vary from day to day; it is also recognized that some of the fluctuations may have occurred spontaneously. However, a consistent

TABLE 3.—EFFECT OF PYRIDOXINE HYDROCHLORIDE ON LEUKOCYTE AND POLYMORPHONUCLEAR NEUTROPHIL COUNTS.

Case	*Weeks of Treatment*	*WBC. per.cu.mm.*	*Neutrophils %*	*Antithyroid Drug and Daily Dose*	*Pyridoxine HCl Daily Dose*
1	0	7,500	53	Thiouracil 400 mg.	
	2	6,800	33	" "	100 mg.
	3	10,800	55	" "	100 mg.
	4	8,600	51	" 200 mg.	Discontinued
	11	7,500	32	" "	60 mg.
	13	6,550	51	" "	60 mg.
	25	7,100	53	" 100 mg.	Discontinued
	27	5,950	44	" "	Calcium lactate 1 gm.
	28	5,600	43	" "	60 mg.
	29	6,800	54	" "	60 mg.
		6,600	57	Thiouracil 200 mg.	
	5	4,100	28	" "	150 mg.
	6	7,550	58	" "	150 mg.
	8	8,350	51	" "	Discontinued
	18	7,200	39	" "	60 mg.
	19	7,200	55	" "	Discontinued
	22	7,300	47	" "	60 mg.
	24	7,450	60	" "	60 mg.
3	0	7,850	48	Thiouracil 200 mg.	
	2	15,500	26	" "	60 mg.
	4	11,200	53	" "	Discontinued
	10	14,450	27	" "	60 mg.
	12	8,600	44	" "	Discontinued
	0	7,800	44	Propylthiouracil 200 mg.	
	1	6,100	31	"	75 mg.
	2	6,150	52	"	75 mg.
5	0	9,000	42	Propylthiouracil 150 mg.	
	1	6,150	30	"	75 mg.
	3	5,900	48	"	75 mg.
6	0	9,500	65	Propylthiouracil 200 mg.	
	1	6,900	40	"	75 mg.
	2	13,400	61	"	Discontinued

tendency was noted for the leukocytes and especially the granulocytes to increase with the administration of pyridoxine and to decrease following withdrawal of this compound. Space does not permit the detailed protocols in all the cases studied; the results in 6 representative cases are shown in Table 3. Case 1 demonstrates that the granulocyte depression did not vary directly with the amount of thiouracil administered; the granulocytic response to pyridoxine is noteworthy. It also shows the persistence of the granulocytopenia when a placebo was used in place of pyridoxine. Case 2 shows the increase in granulocytes with pyridoxine and the decrease

whenever pyridoxine was withdrawn. This patient received pyridoxine at frequent intervals, practically throughout the complete course of thiouracil treatment; this case has now shown a remission of over 3 years since the drug was discontinued. Cases 4, 5 and 6 illustrate the development of an appreciable degree of granulocytopenia with propylthiouracil and the improvement coincident with administration of pyridoxine.

In this series, 7 patients developed granulocytopenia while on propylthiouracil therapy, and 19 on thiouracil. A granulocyte response followed administration of pyridoxine in almost every case. In 3 instances, the anti-thyroid drug had to be abandoned because of a disturbing drop in granulocytes in spite of pyridoxine administration; yet in each of these a significant though inadequate response to this drug was noted. It is conceivable that in these patients, the amount of pyridoxine prescribed may have been insufficient.

Summary and Conclusions. 1. Thiouracil or propylthiouracil, when administered to patients with toxic diffuse goiter in adequate amounts daily for approximately 1 year, produced remissions for 6 months or longer after the drug was discontinued in 30 of 39 cases (77%). Of the 39 cases, 25 (64%) have had remissions for longer than 1 year.

2. Propylthiouracil may be used effectively for periods longer than one year in patients who: a) refuse thyroidectomy in spite of relapse, b) continue to relapse but surgery is inadvisable, or c) have serious complicating disorders so that interruption of treatment is hazardous.

3. In 18 patients with thyrotoxic exophthalmos, no single instance of progressive exophthalmos was noted during the administration of these thiourea derivatives. In 9 cases (50%), the proptosis receded partially or completely.

4. In 13 of 27 cases (48%), the administration of thiouracil or propylthiouracil was accompanied by a decrease in the size of the thyroid gland; in 12 cases (45%), the size of the goiter remained unchanged; in 2 cases (7%), the thyroid gland enlarged during the course of therapy.

5. Pyridoxine hydrochloride, administered orally, acted as a granulocytic stimulant in those patients who developed leukopenia or granulocytopenia during the administration of these compounds.

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INTRAVENOUS USE OF QUINIDINE, WITH PARTICULAR REFERENCE TO VENTRICULAR TACHYCARDIA

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Quinidine has been used successfully in the treatment of ventricular tachycardia since 1922[1,2,4,5,8-16,18,19,22,30,32-35,37-39]. Despite statements by Kerr[20] to the effect that the results are inconclusive and that it should not be used following myocardial infarction, the present trend of opinion is well expressed by Herrmann and Hejtmancik[19], who state, "It (quinidine) has come to be regarded as a specific in the control of paroxysmal ventricular tachycardia. . . .". Its use following myocardial infarction, long advocated by Levine[21], is not based on clinical findings alone since Smith and his co-workers[31] found that quinidinized dogs survived coronary ligation better than the control animals.

Ventricular tachycardia, with but rare exceptions[6,7,17,23], is a manifestation of severe myocardial damage or, less frequently, digitalis intoxication. Occurring following myocardial infarction, it is of grave significance and its presence constitutes an emergency. If allowed to continue it may lead to 1) ventricular fibrillation, 2) asystole, or 3) cardiac failure.

Oral administration of quinidine is not always possible due to the inability of the patient to take the drug because of vomiting or loss of consciousness. Frequently, because of the critical condition of the patient, a more rapid method of induction is desired. For these reasons, quinidine and certain quinine compounds have been given intramuscularly[4,28,35] and intravenously with various results. While others have made general statements on the subject[20,22,26,36,37], the literature regarding the use of quinidine intravenously has been summarized in Table 1[1,2,3,5,8,11,12,18,19,28,32,34,38].

In general, quinidine has been given

TABLE 1.—SUMMARY OF THE LITERATURE ON INTRAVENOUS USE OF QUINIDINE

	Drug	*Dosage in grams*	*Number of cases*	*No. of reactions*	*Type of reaction*	*Number P.V.T.*	*Number reverted*
Armbrust-Levine	QS	0.2–1.5	31	4	See text	31	20
Arrillaga-Soldati	QS	0.5–2.0	6	0		4	2
Askey	QS	1.5	1	0		1	0
Bunn	QDHCL	0.5	1	0		1	1
Chapman	QL	0.65–1.3	2	1	A-C-R	2	1
Collins	QL	0.2–0.4	25	0		1	1
Dubbs-Parmet	QS	0.5	1	0		1	1
Etala-Berreta	QS	1.0	1	0		1	1
Hepburn-Rykert	QS	1.3	9	1	CY-S-R	9	9
Herrmann-Hejtmancik	QS	1.7	3	0		3	1
Riseman-Linenthal	QDHCL	0.5	1	1	T-U-R	1	0
Stempien-Katz	QDHCL	0.3	1	0		1	0
Strong-Munroe	QS	0.6–2.0	1	1	V-C-U-R	1	1
Williams-Ellis	QDHCL		1	0		1	1
This series	QL	0.4–3.25	13	3	N-V-R	4	3
Totals			97	11		62	42

QS—Quinidine sulph
QDHCL—Quinine di-HCl
QL—Quinidine lactate
A—Asystole
C—Convulsions
CY—Cyanosis
N—Nausea
V—Vomiting
S—Shock
T—Tinnitus
U—Unconsciousness
R—Recovery

intravenously because of the patient's critical condition and the necessity for rapid action, or because the patient was unable to take the drug by mouth. Collins[9] has used the drug in 25 patients during surgical operation because of the occurrence of cardiac arrhythmia.

In the 31 cases of Armbrust and Levine[1], in which quinidine was given intravenously, 4 died shortly after the medication. The authors state that these 4 deaths were due to quinidine toxicity and yet point out that each patient was moribund at the time the injection was given. Chapman[8] reported 1 patient whose heart stopped, following which there were convulsions, vomiting, and recovery. This occurred following the use of intravenous quinidine lactate. One patient of Hepburn and Rykert[18] became restless, cyanotic, and went into shock following 0.6 gm. of intravenous quinidine sulfate. Padilla and Cossio[26] attributed lassitude, pallor, cold sweat, and impaired vision occurring after intravenous quinidine to the return to normal rate and rhythm. Riseman and Linenthal[28] reported tinnitus and unconsciousness in one patient following intravenous quinine dihydrochloride. The patient reported by Strong and Munroe[34] vomited, had a convulsion, and became unconscious. The patient reported by Etala and Berreta[12] had severe convulsive seizures 48 hours following 4 gm. of quinidine intravenously over a period of 4 days. After an episode of paroxysmal ventricular tachycardia 2 years later, in which regular sinus rhythm was restored after 1 gm. of quinidine intravenously, the patient died in shock, the time following the intravenous quinidine not being mentioned.

COMBINATION WITH OTHER DRUGS. Several authors[2,19] have found quinidine effective in abolishing ventricular tachycardia only when given with intravenous digitalis or one of its derivatives. Others mentioned the beneficial effect of atropine. Stempien and Katz[32] treating 1 patient with paroxysmal ventricular tachycardia found intravenous quinine dihydrochloride alone and with atropine ineffectual. When potassium chloride was added, the rhythm promptly returned to normal.

Method of Administration. Quinidine lactate is pharmacologically similar to the sulfate. It is, however, much more soluble and is stable in solution. It is supplied in 10 cc. ampoules, each containing 0.65 gm. of the drug*.

Because of previous experience with the intravenous use of quinidine sulfate according to the method of Hepburn and Rykert[18], the first few patients treated received the drug as follows:

The contents of 6 ampoules (3.9 gm.) were added to 500 cc. of 5% glucose and the solution was given intravenously at the rate of about 100 cc. per hour. This was discontinued immediately upon obtaining the desired effect or upon any signs of toxicity. Since the average patient required less than the full 3.9 gm., and since the ampoules were manufactured to contain 0.65 gm. in 10 cc., the method soon was changed whereby the contents of one ampoule were added to 50 cc. of 5% glucose in a 100 cc. flask, the mixture being given intravenously at approximately 2 cc. per minute. Should a larger dose be needed, this solution could be replenished and the administration continued uninterrupted.

Whenever possible, a test dose of 0.2 gm. of quinidine sulfate was given orally to rule out sensitivity to the drug. In some cases, however, the condition of the patient was so serious that intravenous quinidine was given as a last resort and time was not available for a test dose.

INDICATIONS. The following were considered to be valid indications for the intravenous use of quinidine:

1. A critically ill patient, usually with ventricular tachycardia, in whom oral quinidine had been ineffective or whose condition was so serious that

* The quinidine lactate used in this study was generously supplied by Dr. Kenneth C. Kohlstaedt, of Eli Lilly and Company, Indianapolis, Indiana.

there was no time for trial of the drug by mouth.

2. A patient in whom surgery of the chest or heart, of a type necessitating cardiac manipulation, was to be performed. In such cases, the patient was given oral quinidine pre-operatively. If tolerated, quinidine lactate was added to the intravenous fluids during operation.

Report of Cases. CASE 1 (82774). A 53 year old white male developed tachycardia (with a rate of 250) 11 days following an acute posterior myocardial infarction (Fig. 1A). A test dose of quinidine sulfate caused no undue effects. Two hours later, his rate still being 250, 2.6 gm. of quinidine lactate in 250 cc. of normal saline was started intravenously. One and a half hours after this was begun, he vomited 200 cc. of clear fluid. Three and a half hours after the solution was started intravenously, the pulse was 100 and the rhythm was regular sinus rhythm (Fig. 1B). On the following morning, the pulse was 84 and the rhythm regular. He was given quinidine sulfate by mouth in gradually decreasing doses. The remainder of his convalescence was entirely uneventful and at the present time he is living and well.

CASE 2 (79723). A 56 year old white male showed auricular flutter 2 days following an acute posterior myocardial infarction. Quinidine sulfate was given by mouth in increasing doses and on the 4th day following infarction, the rhythm was markedly irregular due to ventricular tachycardia. The dose of quinidine at that time was 0.6 gm. every 3 hours by mouth. On the following day, 5 days after infarction, the ECG showed further changes, and because of the serious-

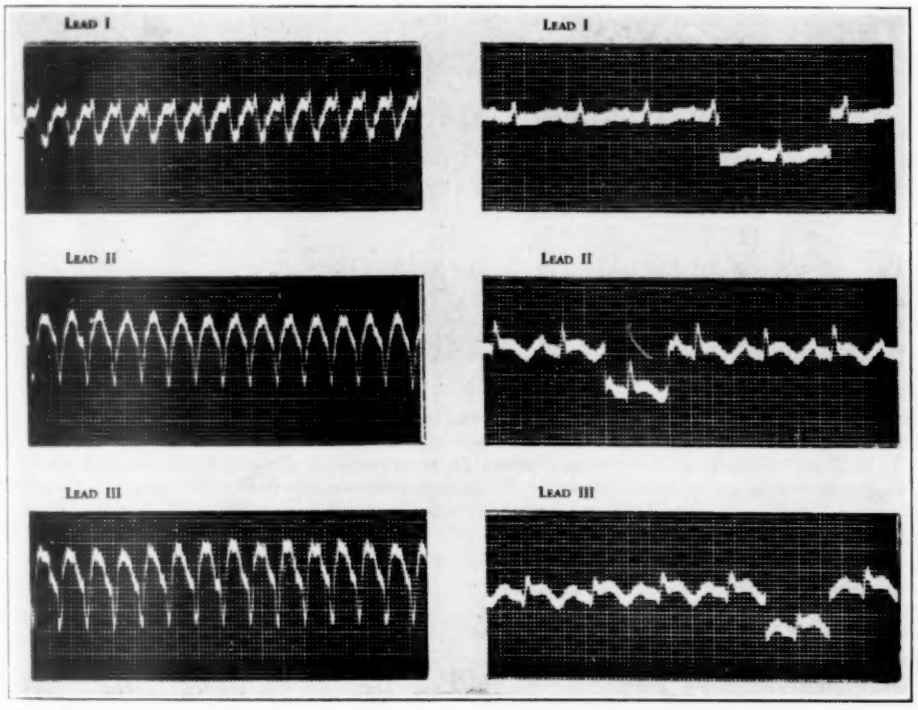

FIG. 1. CASE 1 A.—Leads 1, 2, and 3, showing tachycardia with rate of 250. While auricular flutter with 1:1 block cannot be ruled out, the rhythm quite likely is ventricular tachycardia. B.—The same leads taken 6 hours after A and after 2.6 gm. of quinidine lactate intravenously, showing regular sinus rhythm, rate 98. The PR interval exceeds 0.24 second but cannot be measured exactly as the P wave is superimposed upon the preceding T wave. Evidence of posterior infarction is present, as it was in serial tracings taken prior to the attack of tachycardia.

ness of his condition 3.25 gm. quinidine lactate in 500 cc. of 5% glucose in water was given intravenously at a very slow rate. At no time did he show any toxic reaction to the drug. Following this medication, the pulse dropped from 160 and irregular to 88 and regular. Quinidine was continued by mouth in gradually decreasing doses. At the present time, 14 months following the infarction, the patient is well and has resumed his job as dishwasher.

lactate was given by vein. The pulse became 96 per minute and regular after this amount had been given, an ECG showing return to normal rhythm (Fig. 2). Since the ECG showed a QRS of 0.14 second, the quinidine was discontinued. On the 4th hospital day the pulse again was 160, the ECG showing ventricular tachycardia. He again was given intravenous quinidine lactate, the rate dropping to 95 with regular sinus rhythm after 0.8 gm. had been given. Later the same day,

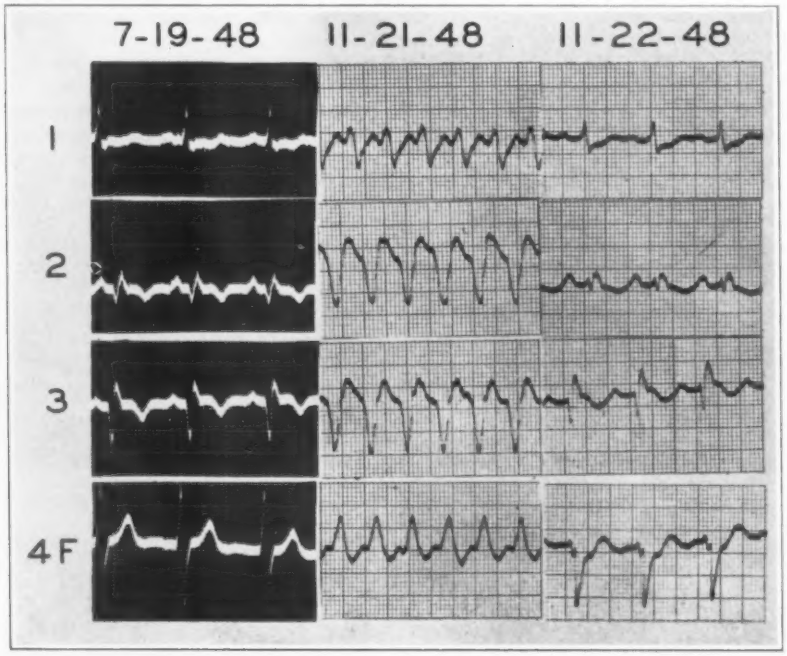

FIG. 2. CASE 3. A.—ECG on 7-19-48, showing evidence of posterior myocardial infarction. B.—ECG on 11-21-48, showing ventricular tachycardia. C.—ECG on 11-22-48, showing sinus rhythm. There is evidence of the old posterior infarct with suggestion of a more recent anterior infarction when compared with previous tracings. The QRS of 0.14 second may be due to quinidine.

CASE 3 (3818). A 52 year old white male had an acute anterior myocardial infarction 6 months following an acute posterior infarction (Fig. 2). His family physician digitalized him following the second infarction. When seen 5 days later, his pulse was 185 and irregular, the ECG showing the rhythm to be ventricular tachycardia (Fig. 2). The digitalis was discontinued and, on the 1st day in the hospital, 1.4 gm. of quinidine was given by mouth. On the 2nd hospital day, 6 days after the infarct, the oral quinidine being ineffectual, 1.95 gm. of quinidine

the pulse became very irregular and the ECG showed ventricular tachycardia. Quinidine was continued by mouth but in very small doses and, on the 6th hospital day, the ECG showed nodal rhythm. This disappeared on the next day. On the 8th hospital day, 3 days after receiving his last dose of intravenous quinidine, the patient suddenly expired. Autopsy showed an old, healed posterior myocardial infarction and a recent anterior infarction. Mural thrombi were present in the left auricle. There was marked

coronary artery sclerosis and bilateral pleural effusion was present.

Case 4 (5275). A 56 year old white male, a known alcoholic, was admitted with an acute surgical abdomen. On the first post-operative day, his pulse was found to be 160 plus, and the rhythm auricular fibrillation. Since his condition was critical, 0.6 mg. Cedilanid was given intravenously but was discontinued when the ECG showed runs of regular sinus rhythm interrupting the auricular fibrillation. This effect, however, was temporary and 0.8 mg. Cedilanid was given intravenously ½ hour later. There being no effect whatsoever on the pulse, 0.65 gm. quinidine lactate was added to his intravenous fluids. This dose was repeated 3 and 6 hours later. After the last intravenous dose, his pulse reverted to regular sinus rhythm with rate of 88. He had no symptoms or signs at any time suggesting quinidine toxicity. He received no more quinidine, his rate remaining regular while receiving 0.2 mg. Cedilanid once daily in his intravenous fluid. He expired on his 4th post-operative day, the autopsy revealing the cause of death to be acute pancreatitis. He had not received quinidine in any form for 3 days.

Case 5 (3472). A 31 year old white male with rheumatic heart disease was admitted to the hospital with subacute bacterial endocarditis and an irregular pulse due to frequent runs of ventricular tachycardia. Although there were signs of beginning cardiac failure, digitalis was withheld because of the cardiac irritability as manifested by the ventricular tachycardia. On his 8th hospital day, the irregularity becoming much more persistent, he was given 3.0 gm. of quinidine by mouth. Since he was vomiting and the amount of the drug being absorbed was questionable, he was given 0.65 gm. quinidine lactate in 50 cc. of 5% glucose by slow intravenous drip. This dosage was repeated every 3 hours for 4 doses, but his pulse became increasingly irregular and he expired 4 hours after the last dose. Autopsy was not performed.

Case 6 (78718). A 65 year old white male was admitted to the hospital in cardiac failure. His heart rate was 170 and the mechanism was supraventricular tachycardia. Carotid sinus pressure, Mecholyl, and digitalis were ineffectual in controlling the rhythm. Quinidine sulfate by mouth, 0.4 gm. every 3 hours, had no effect upon the pulse. As a last resort, he was given quinidine lactate by slow intravenous drip. After approximately 0.4 gm. had been given, the patient became nauseated and vomited. The intravenous administration was discontinued and the drug continued by mouth. Later, this patient was found to have widespread bronchogenic tuberculosis and, after treatment with streptomycin, the patient showed improvement and the pulse became controlled.

Case 7 (82359). A 71 year old white male had carcinoma of the gastric fundus involving the cardia and lower esophagus. On the 2nd post-operative day, following a thoraco-abdominal splenectomy, total gastrectomy with esophagojejunal anastamosis and entero-enterostomy, his pulse remained between 130 and 160 per minute, the rhythm being sinus tachycardia. As a last resort, he received 0.65 gm. quinidine lactate in his intravenous fluids at 12-hour intervals for 3 doses. While there was no visible effect upon the pulse, there also were no toxic signs or symptoms present. Autopsy showed the death to be due to a closed loop duodenal obstruction.

The next 4 cases were given quinidine lactate in their intravenous fluids during operation because the nature of the operation entailed cardiac manipulation. These patients withstood their operative procedures well and showed no cardiac arrhythmia at any time.

Case 8 (49738). A 70 year old white male with carcinoma of the esophagus had a thoracic, total thoracic esophagectomy with supra-aortic esophagogastrostomy. He received quinidine sulfate, 0.2 gm. every 3 hours for 16 hours pre-operatively. During the 10-hour operative procedure, quinidine lactate was added to his intravenous fluids so that he received approximately 0.2 gm. every 3 hours. The patient showed no cardiac irregularity, even at the time of mobilization of the aortic arch, and his immediate post-operative course was excellent. The quinidine was discontinued on the first post-operative day. The patient expired on his 18th post-operative day from a sudden hemorrhage.

Case 9 (82875). An 82 year old white female with carcinoma of the mid-thoracic esophagus had a thoraco-abdominal, total thoracic esophagectomy with supra-aortic esophagogastrostomy and splenectomy. After showing no reaction to a test dose by mouth, 0.65 gm. quinidine lactate was given intravenously the evening before operation and was repeated during the operation. Her post-operative course was uneventful until the 9th post-operative day when her pulse began to rise. Being uncontrolled by any other means, she was given 0.3 gm. quinidine lactate twice daily with her intravenous fluids.

This was continued for several days and while there were no signs or symptoms at any time of quinidine toxicity, there was no effect upon her tachycardia.

Case 10 (81880). A 56 year old white male with carcinoma of the esophagus was given quinidine lactate for the same reason and in the same manner as in Case 8. There were at no time any signs or symptoms of quinidine toxicity, and the patient's pulse remained regular throughout the course of his hospitalization.

Case 11 (70393). A 33 year old white male with severe mitral stenosis and hemoptysis had an operation directly upon his mitral valve in an attempt to relieve his symptoms. He received quinidine intravenously pre-operatively, during the operation, and on the first post-operative day. At no time did he show any signs or symptoms of quinidine toxicity and his pulse remained regular except at the instant the operator was in the lumen of the mitral valve. The patient left the hospital, improved, several weeks following the operation.

Case 12 (85244). A 53 year old woman had extensive carcinoma of the cervix for which a total pelvic evisceration was done on November 23, 1949. Her pre-operative ECG showed evidence of an old anterior myocardial infarction, but there was no evidence of any active myocardial lesion or of ventricular failure. On the 10th post-operative day, she developed a cardiac irregularity which was apparently due to runs of premature beats. This was never confirmed electrocardiographically due to its transient nature. On that day she received 0.325 gm. quinidine lactate intravenously, and 2 days later, the same dose on 2 occasions. The irregularity subsided and the patient left the hospital with no further evidence of cardiovascular disease. She is living and apparently well at this date.

Case 13 (85353). A 65 year old white woman with a chief complaint of dysphagia beginning in October 1949. Examination revealed this to be due to carcinoma of the esophagus. She was admitted to the hospital on November 25, 1949, for operation. On the day of admission, she developed an acute anterior myocardial infarct. Her progress was uneventful. The question of operation was given much consideration and, because of the danger of metastases, she was operated upon on January 11, 1950, with a total resection of the esophagus, a partial gastrectomy and splenectomy, and supra-aortic esophagogastrostomy. Two days prior to operation, a test dose of 0.2 gm. quinidine sulfate was given without any reaction. During the 11-hour procedure, she received 2 doses of quinidine lactate, 0.65 gm. each added to 1000 cc. of fluids. She received 0.65 gm. in her intravenous fluids at midnight, the same dose on her 2nd post-operative day, and 0.65 gm. quinidine lactate intravenously on 3 separate occasions on the 3rd post-operative day. Following operation, signs of cardiac failure appeared. Digitalis was withheld, however, because of the recent myocardial infarction, until the 3rd post-operative day at which time she was digitalized with Cedilanid. Despite this measure, she expired on the 4th post-operative day, autopsy revealing congestion of both lung bases and an incompletely healed anterior myocardial infarct.

Discussion. The efficacy of quinidine in the treatment of paroxysmal ventricular tachycardia has been established by others. The purpose of this study was to determine the relative safety of quinidine lactate when given intravenously.

In the 13 patients treated, the dose varied from 0.4 gm. (Case 6) to 3.25 gm. (Case 2). The smallest dose given to a patient with paroxysmal ventricular tachycardia which was followed by return to regular sinus rhythm was 0.8 gm. (Case 3). Three patients became nauseated and vomited during or immediately following the intravenous administration of 0.4 gm. (Case 6), 0.65 gm. (Case 5), and 2.6 gm. (Case 1). There were no other signs or symptoms even slightly suggestive of quinidine toxicity in the series of over 30 intravenous doses given the other 8 patients. In this clinical study, as in others, it is most difficult, if not impossible, to differentiate phenomena as being secondary to the medication or to the disease. Patient 5 had vomited on several occasions before receiving quinidine. Since nausea and vomiting are by no means specific reactions, their occurrence alone should not be interpreted unequivocally as evidence of a reaction to quinidine. Asystole, convulsions, cyanosis, shock,

impaired vision, and unconsciousness were not encountered in this series of patients. It is possible that many of the severe reactions described in the literature were the result of the disease, impurities in, or too great a concentration of, the intravenous solution, or its too rapid administration. Unfortunately, it is impossible to prove or disprove this theory.

Some authors[4,35] prefer intramuscular to intravenous quinidine therapy, claiming that the former is less dangerous. Admitting the potential danger of both, I prefer the latter because when properly administered (well diluted and given *slowly* under constant observation) intravenous quinidine lactate can be discontinued immediately upon the restoration of normal rhythm or the first sign of toxicity. Quinidine given intramuscularly, on the other hand, is not subject to such control and the dose, once given, must be allowed to continue for its full effect.

Conclusions. Quinidine lactate, a soluble, stable, and pharmacologically effective quinidine salt, is suitable for intravenous use. Ten cc. of a solution containing 0.65 gm. quinidine lactate should be added to 50 cc. of 5 per cent glucose and the mixture allowed to enter a vein at a rate not exceeding 2 cc. per minute. Under constant observation, its administration can be discontinued immediately upon re-establishment of regular rhythm or upon the onset of any toxic reaction. Given in this manner, it is relatively safe and may well be lifesaving, particularly in patients developing ventricular tachycardia following myocardial infarction in whom regular sinus rhythm cannot be re-established by oral quinidine, or whose condition is so critical as to demand the greatest possible speed of action.

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CHLOROMYCETIN TREATMENT OF TYPHOID FEVER
REPORT OF TWO CASES

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With the recent advent of chloromycetin and its seeming specificity in acute typhoid fever, it seems worthwhile to describe the course in 2 cases treated with it. The basic work of Burkholder[2] in isolating the drug, and Woodward and Smadel's[5,6,8] original reports on its clinical effectiveness in typhoid fever and rickettsial diseases, prompted its use. More recently, Woodward and Smadel[7], and Bradley[1] have confirmed its chemo-therapeutic activity.

Case Reports. Case 1. G.N., a 59 year old Oriental male, was admitted with the chief complaint of watery diarrhea of 1 week duration. The onset was explosive, averaging 20 to 25 bowel movements a day, gradually decreased to 7 the day of admission. Associated symptoms included chills, fever, diaphoresis, weakness and malaise. There was no abdominal pain, nausea, vomiting, hematemesis or melena, nor any skin rash or icterus. Otherwise the present and past history were non-contributory.

Physical examination revealed a well nourished Oriental male, appearing acutely ill, somewhat disoriented and irrational. The skin was clear, but warm and dry. The blood pressure was 110/68, pulse 96, respirations 15, and the temperature 104.2°F. The conjunctivae were of good color. There was no icterus or petechiae. The tongue was coated. There were a few fine, subcrepitant bibasilar pulmonary rales, but percussion, tactile and vocal fremitus were normal. The heart was enlarged moderately to the left and down, and a Grade 2 systolic murmur was heard over the precordium, loudest at the base. The abdomen was not tender, and no masses were palpable. No skin rash was noted. Rectal and other examinations were normal.

A hemogram revealed white cells of 11,500 (81% neutrophils, 17% lymphocytes, 2% monocytes); red cells 3.9 million and 10 gm. hemoglobin (Sahli). The urine was not remarkable save for 2+ albumin and occasional white cells and hyaline casts per high power field. B.U.N. was 8 mg. per 100 cc., creatinine 1.8 and sugar 120. On the 5th day, a stool culture was reported positive for *E. Typhosa*, and Typhoid O and H agglutinins positive in greater than 1:640 dilution, Paratyphoid A and B in 1:40, Proteus OX 19 in 1:20, Brucella abortus O.

A septic fever prevailed for the first hospital week, and the symptoms persisted unabated. A 4 day course of sulfathalidene had no effect. Chloromycetin was begun on the 7th hospital day; initial dose was 2.5 gm. and maintenance of .25 gm. every 2 hours. Within 2 days the patient appeared much less toxic, he was rational and taking food well. The fever defervesced by lysis over a 4 day period and then remained normal. The stools remained watery green although but 3 per day. After 7 days chloromycetin was decreased to 0.25 gm. every 4 hours, and maintained for another 2 weeks.

Further blood cultures were sterile; however stool cultures were positive for *E. typhosa* 4 and 6 days after starting chloromycetin. Thereafter they were negative.

Convalescence was uneventful and the patient was discharged on the 28th hospital day. The graphic record is presented in Fig. 1.

Case 2. V. D., a 20 year old colored female, was admitted with the chief complaint of severe headache for 1 day, and a 3 day history of dizziness, nausea, vomiting, chills,

fever and sweating, and 11 days of vaginal bleeding following a normal menstrual period. The drinking water on a visit to South Carolina, 2 weeks previously, was obtained from a well located near an outdoor privy. There was no diarrhea, melena, hematemesis or jaundice. The system review was otherwise negative. The past history was noncontributory.

Physical examination revealed an acutely ill, young, colored, adult female. The blood pressure was 124/96, respirations 28, pulse 112, temperature 105°F. There was no icterus, petechiae, or generalized glandular enlargement. The skin was clear, no rose spots present. Heart and lungs were normal. No abdominal masses were palpable. Voluntary splinting of the abdomen was noted, the right side more than the left. The physical examination was otherwise not remarkable.

Blood cultures, taken on the 3rd and 4th days were positive for *E. typhosa*. Agglutinins for Typhoid O was positive in 1:80 dilution and H-1:40. Repeated blood, urine, and stool cultures were negative.

During the severe febrile course of the first hospital week, the patient became mentally confused and stuporous. On the 9th hospital day, chloromycetin was begun with dose of 0.25 gm. every 2 hours. A dramatic an initial dose of 2.5 gm., and a maintenance response was noted. The patient appeared less confused and somewhat stronger within 24 hours. By the third day of therapy, the temperature was normal, where it stayed for the remainder of the hospital course. On the 4th day, chloromycetin dosage was decreased to 0.25 gm. every 3 hours, and maintained to the 18th day of specific therapy, when it was discontinued.

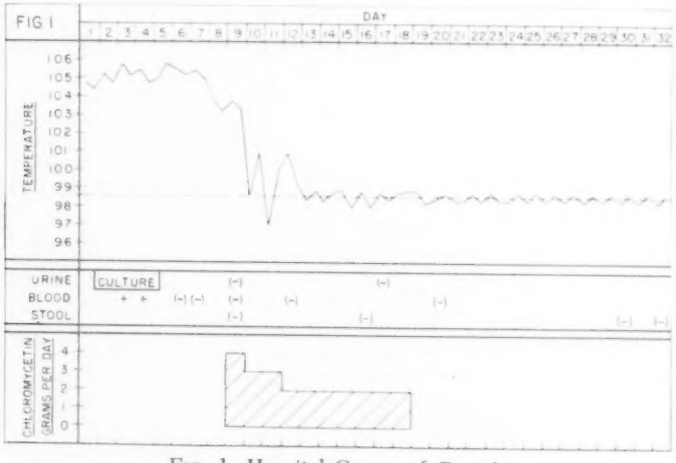

FIG. 1. Hospital Course of Case 1.

On admission, a hemogram revealed white cells 12,360, red cells 4.8 million, hemoglobin 12.5 gm. Sedimentation rate (Cutler) was 18 mm. in 15 minutes. Urine was alkaline, and showed a specific gravity of 1.020, a trace of albumin, and no sugar. Chest Roentgen-ray revealed decreased radiability of the right lung field. Empirically, penicillin and streptomycin were begun on admission and continued for 2 days. On the second hospital day aureomycin, 250 mg. 4 times per day, was started, and maintained for 4 days. The patient evidenced no clinical response, and maintained a high plateau fever ranging from 104°F. to 105.8°F. for the first hospital week.

The patient, following the dramatic response to therapy, made an uneventful convalescence over a period of several weeks. She was discharged on the 34th hospital day. The graphic record is presented in Fig. 2.

Discussion. Two patients suffering from acute typhoid fever received chloromycetin therapy, initiated on the 11th and 14th day of the disease, respectively. Both manifested a rapid and dramatic clinical response to therapy. The fever went down by lysis

in from 3 to 4 days. Improvement in the general condition and subsidence in the manifest toxicity were noted as early as 24 hours after instituting specific therapy, and thereafter was progressive and rapid.

Stool culture for *E. typhosa* remained positive 6 days after the onset of chloromycetin in Case 1; in Case 2 blood culture and stool culture were negative at the time of onset of therapy. No relapses, either clinically or via blood or stool were noted. No complications of typhoid fever occurred in either case.

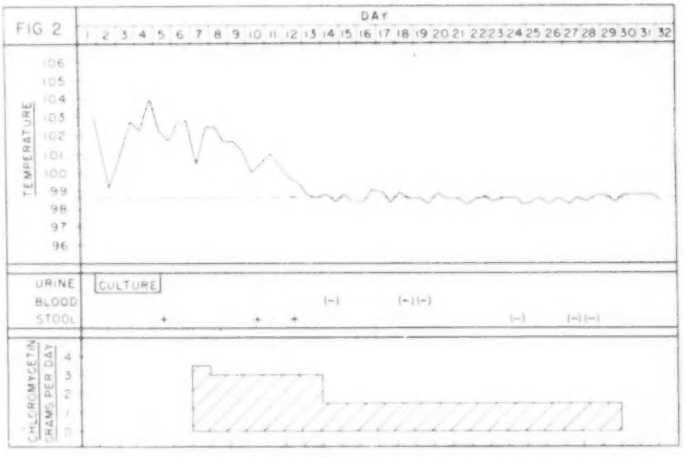

FIG. 2. Hospital Course of Case 2.

A priming dose of 50 mg. per kg. of body weight and a maintenance dose of 0.25 gm. every 2 hours until the fever disappears appears to be adequate. The interval between doses is then increased to every 3 or 4 hours. This should be maintained for a total duration of 2 weeks[7]. No toxic reactions were noted to chloromycetin[3].

Our results are similar to those reported by Woodward[8] and Smadel[7] and the British investigators[1,4]. Chloromycetin appears to be specific in typhoid fever. Therefore, the need for the earliest possible diagnosis in order to institute early therapy, and so reduce morbidity and possible complications, becomes evident.

Summary. 1. Two cases of acute typhoid fever treated with chloromycetin have been described.

2. Rapid lysis of fever in 3 to 4 days, and corresponding subsidence in the toxic condition were observed.

3. Chloromycetin therapy was maintained for 22 and 21 days, respectively.

4. Stool culture in 1 case remained positive 6 days after the onset of chloromycetin therapy. Thereafter, all blood and stool cultures remained negative for *E. typhosa*.

5. No relapses were noted, nor were any major toxic reactions to the drug observed.

6. Chloromycetin appeared to be specific in the 2 cases treated.

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CHRONIC SCHISTOSOMIASIS JAPONICA: DIAGNOSIS BY RECTAL BIOPSY WITH DESCRIPTION OF SIGMOIDOSCOPIC ABNORMALITIES

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The large number of cases of schistosomiasis japonica which occurred among American troops on the island of Leyte, Philippine Islands, in 1944 and 1945 and a comparable number which occurred in Japanese prisoner-of-war camps[20] have served to bring this disease to the attention of the American medical profession. Many of the cases now being seen in the United States have received adequate treatment and the majority of these are probably cured of the disease; however, there are undoubtedly some in whom treatment was not curative. The latter, coupled with those who acquired subclinical infections[2,7,16,20] and received no treatment, frequently present a difficult problem. These patients are often seen with hepatic or central nervous system involvement and schistosomiasis is ruled out on the basis of several negative stool examinations. Skin tests and serological reactions may be of diagnostic value but their efficacy has not been established and misleading results are sometimes obtained[6,25,26]. Later, at operation or autopsy, the characteristic lesions and ova are discovered.

Although ova of *Schistosoma japonicum* are deposited primarily in the wall of the small intestine, the occurrence of polyps and ulcerations of the large bowel in chronic schistosomiasis is well recognized[1,7,17,24]. The literature contains no data as to the incidence of these lesions or as to the various forms they may assume, but recent descriptions of lesions in the rectum and lower sigmoid colon in the relatively acute stages of the disease[15,16] suggest that ova are deposited in these localities more frequently than is generally appreciated and that sigmoidoscopy should reveal visible abnormalities in a large percentage of patients with chronic infections.

Rectal biopsy has been found superior to other methods in the diagnosis of *Schistosoma mansoni* infections and it is often a valuable diagnostic adjunct in schistosomiasis hematobium[9,11,12,13,19,21,22]. In addition, vesical biopsy frequently reveals ova of *Schistosoma hematobium* in the walls

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of urinary bladders which present no gross lesions[10,12]. Aspiration of rectal crypts by means of mechanical suction[14] as well as scraping and biopsy of suspicious lesions in the rectum and sigmoid[7,15,16] have been found of value in the diagnosis of *Schistosoma japonicum* infections and in a recently reported case ova were demonstrated by means of biopsy of the valves of Houston[26]; however, a sufficiently large series of cases has not been studied by the latter method in this disease to establish its superiority over other diagnostic procedures.

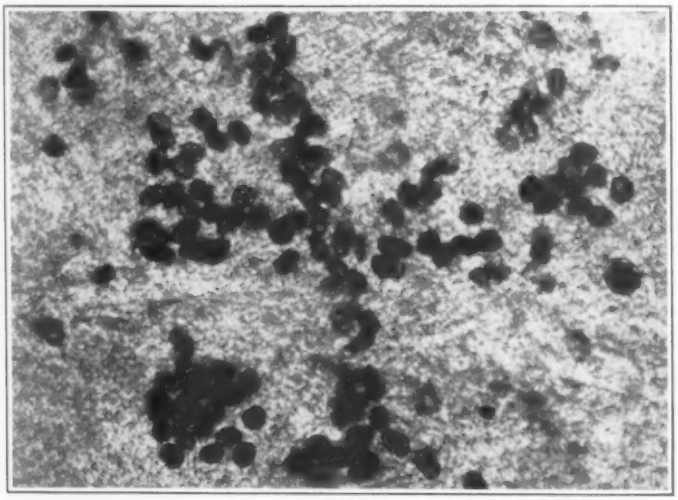

FIG. 1.—*Schistosoma japonicum* ova in semitransparent tissue film (X 40).

The purpose of this report is (1) to compare rectal biopsy and fecal examination as means of detecting *Schistosoma japonicum* infections in natives of endemic regions; (2) to describe the sigmoidoscopic picture produced by long-standing infections; and (3) to give a brief description of the changes observed histologically in the biopsy specimens.

Method of Biopsy and Selection of Cases. Rectal biopsy was performed on 80 Filipino soldiers who had previously resided in endemic schistosomal areas on the islands of Leyte, Samar, and Mindanao[23] and who showed no clinical evidence of acute schistosomiasis at the time of examination. The biopsy specimens were taken from the edge of the second valve of Houston, 10 cm. from the anus, with a laryngeal biopsy forceps. The procedure was relatively painless and was not complicated by prolonged bleeding, perforation, delayed healing or fistula formation. Each specimen measured approximately 4 by 4 mm. and consisted of mucosa and submucosa. Each was compressed firmly between 2 glass slides until a thin, semitransparent film was obtained and then examined under a coverslip with the low and high power of the microscope. Often it was necessary to soften the tissue by immersion in tap water for 3 to 5 minutes, as suggested by Ottolina[21], in order to obtain a film of adequate transparency and to destroy the red blood cells. *Schistosoma japonicum* ova, usually in characteristic clumps and strings, were found in the biopsy specimens from 30 patients.

Sixty patients were selected for further study: the 30 with positive biopsy and 30 of those with negative biopsy. The latter served as a control group in that an attempt was made to discover whether or not these patients had *Schistosoma japonicum* infections not demonstrable by rectal biopsy.

DURATION OF INFECTION. All of the patients had enlisted in the United States Army

approximately 3 years before being examined. Their ages varied from 20 to 38 years, the average being 25 years. The time of residence in endemic schistosomal areas varied from 17 to 34 years for the patients with positive biopsy (average 22 years) and from 4 to 25 years for those with negative biopsy (average 19 years). Sixteen of those with positive biopsy and 13 with negative biopsy had not returned to endemic schistosomal regions since their enlistment; the remainder had returned for short periods 6 to 24 months before being examined.

The majority of the patients with schistosomiasis had probably been infected originally during childhood and subsequently on numerous occasions. A history of repeated wading in rice paddies and fresh water streams was obtained from each of the 60 patients studied, but determination of the exact time of acute schistosomal infections was difficult, primarily because of the multitude of other agents which produce gastrointestinal disturbances and febrile episodes in tropical regions. Nevertheless, none could recall having had prolonged febrile illnesses or urticaria and, although the majority had had one or more mild episodes of diarrhea, only 5 in each group had had dysentery prior to enlistment in the Army. It is unlikely that those who had returned to endemic areas after enlistment had become infected initially during these visits because of the fact that all denied exposure at this time. Hence, it seems safe to conclude that the patients with schistosomiasis had had the disease for at least 3 years and probably much longer.

Stool Examinations. Purged fecal specimens were obtained after administration of 60 cc. of saturated magnesium sulfate solution, no more than 2 stools being collected following each purgation. Four methods of stool examination were utilized:

1. *Direct Fecal Films*[8]. A small amount of feces was mixed with tap water on a glass slide and examined under a coverslip with the microscope.

2. *Acid-Ether Concentration*[3,17]. Approximately 1 gm. of feces was emulsified in 5% acetic acid or 40% hydrochloric acid and the material filtered through gauze into a centrifuge tube. An equal amount of ether was added and the tube shaken vigorously. After centrifugation at 1500 rpm for 2 minutes the debris floating at the acid-ether junction was loosened with an applicator and the acid-ether layer decanted. The sediment was then stirred and a small amount transferred to a slide for examination.

3. *Sedimentation*[8]. A generous portion of stool was comminuted in 5 to 10 parts of chlorine free tap water containing 0.5% glycerine. The mixture was filtered through gauze into a conical glass and allowed to sediment for 30 to 45 minutes. Then the supernatent fluid was poured off and the sediment resuspended. This process was repeated 4 times after which the sediment was centrifuged for 2 minutes at 1500 rpm. A small portion of the final sediment was examined microscopically.

4. *Hatching*[4]. The material obtained by sedimentation was transferred to a 250 cc. Erlenmeyer flask, diluted with tap water containing 0.5% glycerine and allowed to stand overnight. Miracidia were searched for near the surface of the water with a hand lens.

In 13 of the cases with positive biopsy and 12 of those with negative biopsy, from 6 to 10 purged stool specimens were examined by direct fecal films and concentration with 5% acetic acid and ether. Ten purged stools from each of the remaining patients were examined by direct fecal films, concentration with 5% acetic and 40% hydrochloric acid and ether, sedimentation and hatching.

Results. None of the stools from patients with negative biopsy contained *Schistosoma japonicum* ova. On the other hand, ova were found in 2 or more specimens from 8 (26.3%) of those with positive biopsy (Table 1).

The two acid ether concentration techniques were equally reliable methods for the demonstration of *Schistosoma japonicum* ova and proved superior to sedimentation in 4 instances. Direct fecal films were rarely positive and viable ova were not demonstrable by the hatching technique or microscopic examination of those found in the stools and biopsy specimens.

Sigmoidoscopic Abnormalities. Sigmoidoscopy was performed after thorough cleansing of the lower bowel with saline enemas; when any doubt existed as to the findings of the original examination the procedure was repeated. The 30 patients with negative biopsy and 9 of those with positive

TABLE 1.—INCIDENCE OF POSITIVE STOOL EXAMINATIONS IN PATIENTS WITH POSITIVE RECTAL BIOPSY

Methods of stool examination	*Patient*	*Number of stools examined*	*Number of stools containing Schistosoma Japonicum ova*
1. Direct fecal films	SA	10	0
	PP	10	0
2. Acetic acid-ether concentration	PE	10	2
	MC	8	0
	RV	8	0
	AA	8	0
	CP	8	0
	BB	7	0
	IN	7	0
	AC	6	5
	FV	6	2
	LA	6	0
	ED	6	0
1. Direct fecal films	AC	10	9
	IB	10	6
2. Acetic acid-ether concentration	AO	10	2
	NT	10	2
	ER	10	2
3. Hydrochloric acid-ether concentration	GA	10	0
	TP	10	0
	DS	10	0
4. Sedimentation	DG	10	0
	SO	10	0
5. Hatching	FA	10	0
	HT	10	0
	ER	10	0
	FM	10	0
	LP	10	0
	AB	10	0
	AA	10	0
Totals	30	270	30

biopsy exhibited no detectable lesions in either the rectum or lower sigmoid colon. In the remaining 21 patients (70%) with positive biopsy several types of abnormalities were encountered.

The most common alteration was the presence of submucosal nodules which produced pink, shiny elevations of the mucosa. These were found in all the patients with abnormal sigmoidoscopy. In 1 instance there was a single 6 mm. nodule; otherwise the diameter was uniformly 1 to 3 mm. As a rule the lesions were discrete or in groups of 4 to 10. They occurred in varying numbers throughout the rectum and lower sigmoid and were often best seen through the anoscope on the first and second valves of Houston. In 3 patients closely packed groups of 50 to 100 nodules gave a distinct cobblestone appearance and in 3 others the apices of a few of the nodules were devoid of mucosa.

Polypoid lesions were discovered in 5 patients. With the exception of 1 patient in whom only 2 such lesions were visible, these occurred in groups of 5 to 10 as rounded or sessile granulations measuring 5 to 10 mm. in diameter and as finger-like projections covered by mucosa which varied from 4 to 20 mm. in length and from 2 to 5 mm. in diameter. A few of the latter showed bleeding, granular apices. In 2 patients the lesions were palpable by digital examination; in the remainder

they were located higher in the rectum and in the lower sigmoid colon.

A single, red, granular area devoid of mucosa and measuring 1 to 3 cm. in diameter was present in 2 patients; in another there were 2 such lesions. These were elevated above the surrounding mucosa, bled easily on trauma and were confined to the rectum.

Diffuse thickening of the bowel wall and generalized paleness of the mucosa invariably accompanied the polypoid lesions and red, granular area. These changes were less pronounced when only submucosal nodules were seen and were noticeable only in those cases in which there were a large number of nodules. Rarely, hyperemic areas which showed dilated venules in stellate pattern similar to those described in early schistosomal infections[16] were present.

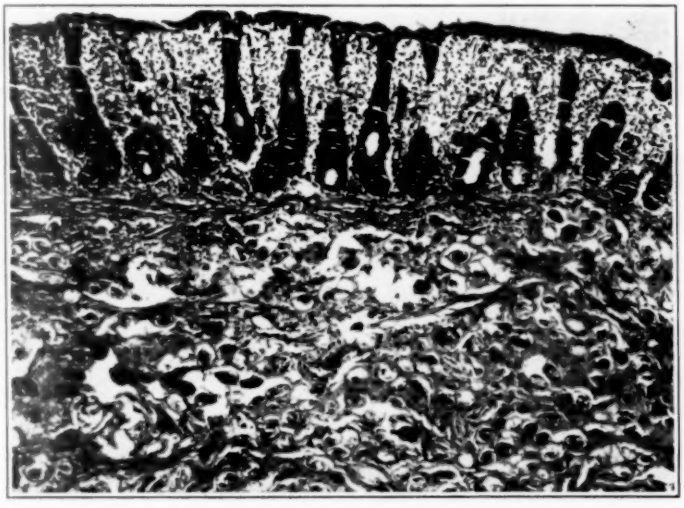

FIG. 2.—*Schistosoma japonicum* ova surrounded by dense collagen in submucosa of rectum (X 40).

HISTOLOGIC OBSERVATIONS. Each of the biopsy specimens found to contain *Schistosoma japonicum* ova was studied histologically. As a rule, ova were as easily demonstrable by this method as by examination of the tissue films. When the infection was light, however, 8 to 14 serial sections were necessary in order to confirm the original observation.

Due to the more abundant deposition of ova in the submucosa than in the mucosa histologic alterations were more pronounced in the former. Two types of lesions, identical with those previously described in chronic schistosomiasis[1,5], were encountered. The most common abnormality was a diffuse fibrous tissue reaction, the ova being embedded in dense collagen with little cellular infiltration. Less frequently they were surrounded by multinucleated giant cells, eosinophils, lymphocytes, monocytes and proliferating fibroblasts which formed pseudotubercles. The ova were frequently distorted, fragmented, hyalinized and sometimes calcified.

EFFECT OF TREATMENT. In addition to the 30 patients with schistosomiasis japonica included in this study, 4 pa-

tients with the disease who received treatment prior to examination have been observed; in each of these the original diagnosis was made by demonstrating ova in the feces. Three patients were Filipino soldiers with chronic schistosomiasis who had received one full therapeutic course of either tartar emetic or fuadin 4 to 6 months prior to examination. Each showed typical sigmoidoscopic findings and positive biopsy. The fourth patient was an American soldier who had contracted the disease on Leyte in 1945 and received 2 courses of tartar emetic and 1 of fuadin. Examination 4 years later disclosed no clinical signs of chronic schistosomiasis, normal sigmoidoscopy and positive rectal biopsy. No ova were demonstrable in the stools of these patients at the time the biopsies were performed and those observed in the tissue films were non-viable.

Summary and Conclusions. 1. Of 80 soldiers who had previously resided in schistosomal endemic areas and showed no clinical evidence of acute schistosomiasis when examined, 30 had positive rectal biopsies.

2. Biopsy of the second valve of Houston has been found superior to fecal examination in the diagnosis of chronic schistosomiasis japonica. Examination of semitransparent tissue films provided the most rapid and accurate method of demonstrating ova in the biopsy specimens.

3. *Schistosoma japonicum* ova were demonstrable in the stools of 26.4% of 30 patients with positive rectal biopsy. No ova were found in the stools of 30 patients with negative biopsy who had lived in endemic schistosomal areas.

4. Sigmoidoscopic abnormalities were present in 70% of the patients with schistosomiasis. These consisted of submucosal nodules, polypoid lesions, red granular areas, diffuse thickening of the bowel wall and dilated venules.

5. Histologically, the ova were more abundant in the submucosa than in the mucosa. The changes observed consisted of pseudotubercle formation and diffuse fibrous tissue reaction around the ova. Hence, in many instances in which ova were demonstrable by biopsy, scraping of the mucosa and mechanical suction would undoubtedly have failed to dislodge those embedded in the submucosa.

6. In 4 patients, treatment with tartar emetic and, or, fuadin did not destroy the ova in the bowel wall. Therefore, repeated biopsies with careful microscopic examination of the ova in the tissue films should provide a valuable means of following patients undergoing treatment, especially when ova are not demonstrable in the stools.

Dr. Edwin S. Gault prepared the photomicrographs. Lt. Marie Happe and Pfc. Ellis Yancey rendered valuable technical assistance.

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OXYGEN THERAPY OF BUNDLE BRANCH BLOCK

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Many excellent studies of the mechanism[8,14,26,27] and the pathogenesis[21,25,29] of bundle branch block have been published. The preponderant opinion concerning the etiology of the condition is that it is an expression of cardiovascular disease, mainly caused by the arteriosclerotic narrowing of a coronary branch supplying the bundle of His[6]. Occasionally, rheumatic heart disease, diphtheria[7,13] and hypothyroidism are found to be the basis for the disturbance and amongst the rarer conditions resulting in this abnormality are congenital heart disease, syphilis, endocarditis[11] and toxicity from drugs, as quinine[22], digitalis and thyroid[19]. On the other hand, in routine electrocardiography, bundle branch block may be discovered in young adults and in middle aged people without any evidence of heart disease[3,9,12,14,15]. Though the possibility of an anomolous course of the distribution of the branches and the terminals of His' bundle might be considered in such cases, yet all instances of bundle branch block cannot be explained on an anatomical basis.

Regardless of the presence or absence of a pathological basis, the electrocardiographic changes can be attributed to a variety of physiological factors. Among these, may be mentioned the fatigue and recovery time of the conduction fibers, the state of nutrition and the degree of oxygenation of the cardiac musculature, the calcium and phosphorus metabolism of the cardiac tissue, and the vagal influence through an increase in the cardiac rate and vasomotor changes, such as induced by sudden fright[15].

Though Oppenheimer[15] and others[25, 28] had pointed out long ago that all patients with bundle branch block do not necessarily have to be considered with such grave prognostic significance and that such people may live many years blissfully unaware of the existence of the condition, yet the treatment of the bundle branch block and its eradication will aid in restoring many more such individuals to a life of comfort and happiness. It is the object of this report to present 3 such individuals, one who was brought from a life of protracted invalidism to a life of usefulness after being subjected to a planned regimen of oxygen therapy, a second woman whose final troubled years on earth were made more comfortable and, lastly, an old gentleman who after 2 critical bouts of illness was enabled to return to his cronies and continue an easier life of philosophic retirement.

Case Reports. Case 1. A 59 year old white mother of 4 children, who had an allergic background of rhinitis, urticaria and migraine, showed no symptoms or signs of cardiovascular disease over a 20 year period of observation. Ten years ago she was helped to hurdle the emotional hump of the menopause with periodic injections of estrogenic substances. During a routine physical examination in 1940, an electrocardiogram showed left axis deviation (Fig. 1a). In December 1946, while enjoying her usual winter vacation in the south, she experienced her first cardiac symptoms. These consisted of a typical attack of angina pectoris; the "contract-

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ing" pain radiating to both shoulders and axillae, accompanied by a cold sweat and palpitation. The pain was so severe that she had "to lie on the bathroom floor" until the paroxysm passed, as suddenly as it had come. Except for weakness, mild sternal oppression and palpitation aggravated after eating or excitement, there were no other complaints. These symptoms were "not bad enough" for her to seek medical aid. She continued her usual activities, which involved managing her household, shopping, swimming, golfing, as well as the emotional strain of helping one of her service-separated sons make a difficult adjustment to civilian life. Though she had 2 more attacks of angina pectoris unrelated to effort she saw no reason to consult her physician until the time arrived for her annual check-up, which was 5 months after the initial episode of precordial pain.

The only unusual feature of her physical examination at this time was a slight cyanosis of the lips. The pulse rate was 80 at rest (128 after excitement). There were no murmurs present. The blood pressure varied from 130/80 at rest to 158/94 after excitement. There was no cardiac enlargement seen either by fluoroscopy or roentgenograms. The thoracic aorta was tortuous and slightly elevated. An electrocardiogram showed a typical left bundle branch block.

She was asked to limit her activities by resting in bed for 18 hours a day and was given small amounts of sedation. She decided that she might recover more rapidly by taking 3 weeks of complete bed rest. After this interval, sensing no subjective improvement and rebelling against a life of semi-invalidism, she asked for a re-examination and re-evaluation of her condition. The bundle branch block had not changed (Fig. 1b). As she had not recovered from the effects of the myocardial damage due to coronary insufficiency and as she showed obvious signs of anoxemia, a trial of 100% oxygen inhalation therapy was suggested.* Accordingly, the patient was supplied with a well-fitting O-E-M mask and oxygen was administered in graduated doses, starting with 40% and quickly increasing the concentration until she was breathing 100% oxygen. When this was accomplished (in less than 2 minutes) an electrocardiogram was taken. The therapy was continued for an hour. The immediate effects were the disappearance of the cyanosis and the eradication of the bundle branch block (Fig. 2b). This occurred within 5 minutes after the start of the treatment. These effects were retained during the entire period of oxygen inhalation. In addition, there was an appreciable lowering of the pulse rate (8 beats per minute) and a drop in blood pressure (from 130/80 to 118/70). Follow-

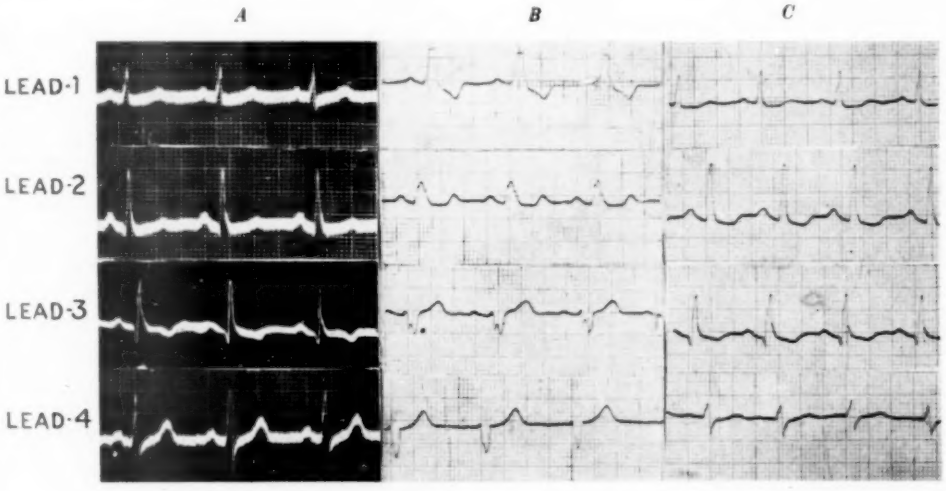

FIG. 1—Electrocardiograms. *a*) 6 years before occurrence of bundle branch block; *b*) 6 months after attack of angina pectoris; *c*) 6 months after cessation of oxygen therapy.

* By Dr. B. S. Oppenheimer.

ing the cessation of the first period of therapy, there was a prompt return of the slight cyanosis. Five minutes after the removal of the mask, the bundle branch block became evident again (Fig. 2c, Lead 4). In view of such a prompt return of the disturbance following cessation of treatment, she was given an hour of oxygen inhalation on awakening, after each meal and at bedtime. The next day, the electrocardiographic study revealed that the abnormal complexes did not appear for ½ hour following cessation of each therapeutic procedure with oxygen. The number of treatments were reduced to 3 times daily: on arising, after lunch and at bedtime. Though ambulatory between periods of treatment, she noted marked subjective improvement. She volunteered the information that her weakness had completely disappeared. Though an electrocardiogram taken 10 days after the initiation of treatment revealed the bundle branch block (Fig. 3a), the period of oxygen inhalation was reduced to ½ hour. After such a 30 minute period of therapy when serial electrocardiograms were taken at 5 minute intervals, to determine the length of time that the beneficial effects of oxygen lasted, it was found that there was a return of the bundle branch block 55 minutes after cessation of treatment (Fig. 3b to 3g). For the next 3 weeks the length of time during which oxygen inhalation was used was kept at a maximum of 30 minutes, and as often as the patient felt she needed it. These occasions were generally on arising, before an afternoon nap and at bedtime. Though she had no pain, she was very apprehensive, and was "excited" very easily. During one such phase of excitement a tachycardia of 160 with a B.P. 170/90 was found to exist, but no precordial pain developed for she was breathing 100% oxygen as a precautionary measure. Twenty hours later (during which interval no oxygen was given) the usual bundle branch block was found (Fig. 4a). On this occasion oxygen was inhaled for only 10 minutes, the mask was removed and electrocardiograms were recorded at 5 minute intervals. It was found at this time that the graphs showed no evidence of conduction disturbance for 65 minutes (Figs. 4c to 4g).

With this information at hand, the period of oxygen inhalation was reduced to a maximum of 10 minutes once a day. One week later, 5 hours following such a short period of therapy, there was still no evidence of bundle branch block.

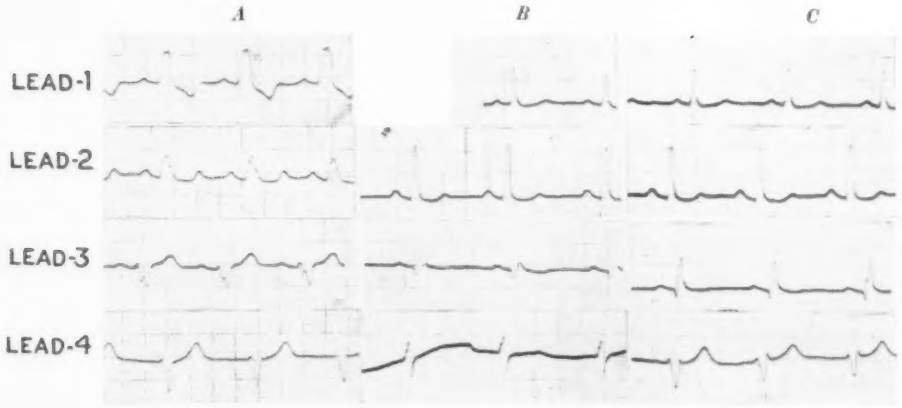

FIG. 2—The initial effect of 100% oxygen therapy: *a*) before inhalation of oxygen *b*) 5 minutes after beginning of oxygen therapy; *c*) 5 minutes after cessation of oxygen therapy.

Oxygen therapy was discontinued entirely. Though, on arising and during excitement, her cardiac rate increased to well above the former critical level that had been accompanied by the intraventricular disturbance, frequent electrocardiographic study revealed no evidence of the return of the bundle branch block (Fig. 5a). After she had been without oxygen therapy for 2 months, an interim when she had motored and traveled by train several hundred miles to elevations up to 1000 feet, electrocardiograms still showed absence of bundle branch block. At this time she performed the 2 step excercise (10 times) without an appreciable increase in her cardiac rate and with the persistence of

normal conduction (Fig. 5b). She has returned to her former pursuits, without experiencing any symptoms of her previous cardiac embarrassment, and electrocardiographic study 6 months after cessation of oxygen therapy revealed normal conduction through the bundle of His (Fig. 1c).

Case 2. In 1932, a 67 year old prematurely senile mother of 3 children complained of palpitation, dyspnea, and pro-

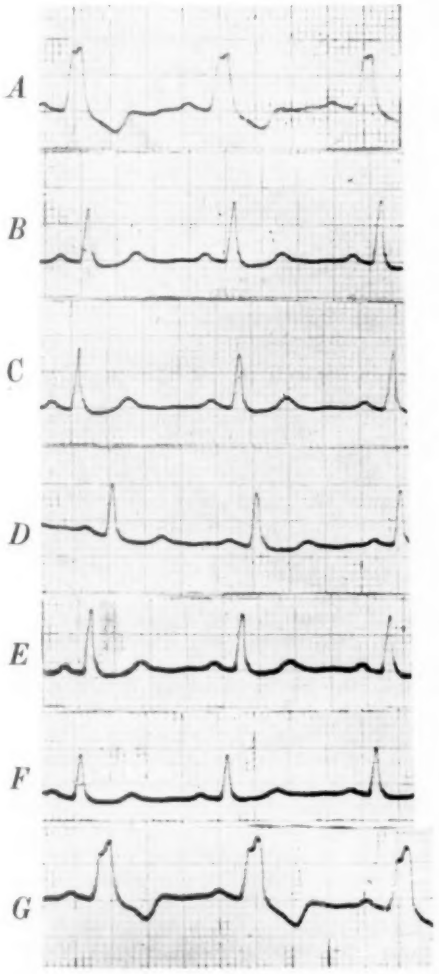

Fig. 3

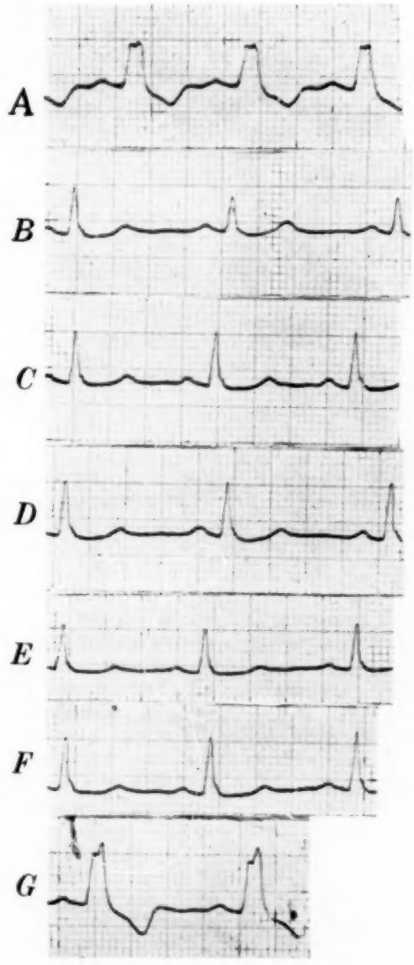

Fig. 4

Fig. 3—Duration of beneficial effect of oxygen inhalation after 10 days of therapy: *a*) before oxygen inhalation; *b*) during oxygen inhalation; 10 minutes after cessation of oxygen therapy; *d*) 20 minutes after cessation of oxygen therapy; *e*) 45 minutes after cessation of oxygen therapy; *f*) 50 minutes after cessation of oxygen therapy; *g*) 55 minutes after cessation of oxygen therapy. (All records are taken with Lead I.)

Fig. 4—Duration of beneficial effects of oxygen inhalation after 1 month of therapy: *a*) before inhalation of oxygen; *b*) during inhalation of oxygen; *c*) 5 minutes after cessation of oxygen inhalation; *d*) 30 minutes after cessation of oxygen inhalation; *e*) 55 minutes after cessation of oxygen inhalation; *f*) 60 minutes after cessation of oxygen inhalation; *g*) 65 minutes after cessation of oxygen inhalation. (All records taken with Lead I.)

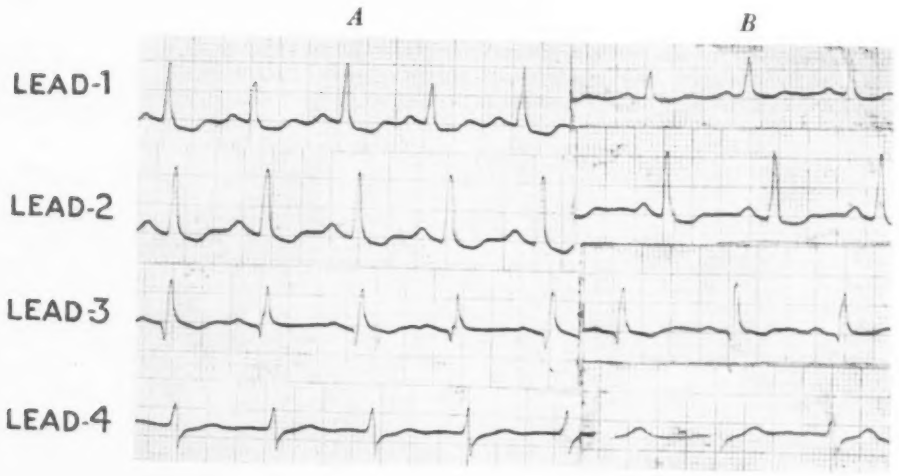

FIG. 5—The results of therapy: *a*) 2 months after cessation of therapy; *b*) following 2 step exercise.

ductive cough of 2 years' duration. She was treated for more than a year with rest and digitalis (Fig. 6a). Since there was no subjective or objective improvement she was admitted to the hospital in Oct. 1933. In addition to her earlier difficulties, she now complained of severe constipation, dysuria with frequency and loss of weight. She was a tiny, emaciated, cyanotic and dyspneic chronically ill woman with tortuous thickened peripheral vessels. The carotids were thickened, and in her eyes, which showed marked arcus senilis, the retinal arteries were thin and tortuous. She was garrulous and uncooperative. Her mentality was abnormal in that her entire emotional life centered itself in her gastrointestinal tract, especially the mouth and anus. Yet, in spite of continued agitation about these problems both during the day and night, she remained free of congestive heart failure. The heart showed marked enlargement with fusiform dilatation and elongation of the transverse arch of the aorta. Roentgen examination of the chest showed a scoliosis of the dorsal spine and bilateral dense pulmonary fibrosis of both apices and displacement of the barium filled esophagus posterior and to the left. The heart rate was regular and alternated, without any external phenomenon, between 60 and 120 beats per minute. There was a moderate hypertension varying from 150/85 to 170/110. An electrocardiogram taken during one of her bouts of palpitation showed left bundle branch block (Fig. 6b). Carotid sinus pressure would cause an immediate drop in her pulse rate without any effect on her blood pressure or the bundle branch block. Though considerable amounts of digitalis over 7 day periods failed to keep her heart rate on an even keel, the pulse varied at a lower level (56 to 100) with digitalis pushed to the point of toxicity than when she was free of digitalis (rate 80 to 130). Usually atropine and amyl nitrate failed to influence the cardiac rate, but when either of these drugs were given, after she had been fully digitalized, there frequently occurred precipitous drops (up to 36 beats) in her pulse rate occasionally to a level of 40 beats per minute. None of these drugs affected the bundle branch block. It was very difficult to administer oxygen to her for any length of time because of the very striking manifestations of the release of her oral and anal eroticism. Yet after 4 days of intermittent oxygen tent therapy, the bundle branch block began to disappear (Figs. 6c and 6d). Oxygen was discontinued the day after sinus rhythm was reestablished and there was no recurrence at the time of her discharge 4 months later (Fig. 6e), or after another 7 months period at the time of her readmission for custodial care (Fig. 6f). During her second hospital admission her heart rate varied from 76 to 124 with the maintenance of sinus rhythm and no signs of cardiac failure.

CASE 3. A 75 year old, lean, white male was admitted to the hospital on February 4, 1949 because of dyspnea, orthopnea and

edema of the lower extremities with involvement of the scrotum. He had been well, except for typhoid fever at the age of 23, until 3 years preceding this admission when dyspnea first appeared. At that time he was working as a gardener when he began to have chest pain which was always produced by effort. This became so severe that finally he had to give up his work. He maintained that he had no swelling of his legs until 1 month before coming to the hospital. Within the 2 weeks prior to admission he developed difficulty in starting his urinary stream. This became so severe that on admission he could pass only a few cc. of urine at any one time. He had been treated at home with digitalis and occasional mercurial injections. On physical examination, he showed marked venous engorgement of his neck veins but no cyanosis. The heart was enlarged to axillary line with B. P. 105/70. The pulse was grossly irregular with a pulse deficit of 10 beats per minute. There was a massive 4+ edema of the lower extremities with edema of the lower abdominal wall and scrotum. The liver was enlarged. There was a marked symmetrical enlargement of all lobes of the prostate. Roentgen-ray examination of the chest showed cardiac enlargement involving all the chambers with proportionate enlargement of the aorta in the superior mediastinum as well as a large calcium deposit in the transverse section of the aortic arch. The bronchovascular markings showed marked congestion. The blood Wassermann was negative. The urine showed concentrating ability varying between 1.010 to 1.025 in spite of an elevated blood urea nitrogen of 55. There was 2+ to 4+ albumin present in the urine without the presence of casts. The electrocardiogram (Fig. 7a) showed auricular fibrillation. He improved so greatly on bed rest, salt poor diet, adequate digitalization, judicious mercurial diuretics and sedation that he was discharged as a bed case after 5 weeks of hospitalization.

FIG. 6—Effect of intermittent oxygen therapy in Case 2: *a*) 2 months before the onset of bundle branch block; *b*) appearance of bundle branch block during an attack of palpitation; *c*) after 4 days of intermittent oxygen tent therapy; *d*) 5 minutes later, still under oxygen therapy; *e*) 5 minutes later oxygen discontinued after establishment of sinus rhythm; *f*) continuation of sinus rhythm 11 months after cessation of oxygen therapy.

He maintained himself quite satisfactorily on the above regimen for nearly 1 year, until 1 month preceding his re-admission on January 3, 1950. In the preceding 4 weeks he was unable to follow his salt poor dietary regimen and did not receive any mercurial diuretics. This time he was markedly cyanotic and orthopneic with massive edema of his lower extremities. He had been able to walk less than 10 feet before dyspnea and weakness would compel him to sit down. He often awakened during his sleep because of shortness of breath to spend the rest of the night in a chair. He had no difficulty in voiding but could pass only scant amounts of urine. In addition to the cardiac enlargement, now there was gross accumulation of fluid in the left thoracic cavity with obliteration of the lower third of the left lung, displacing the heart towards the right side. There was also an accumulation of fluid at the right base. The heart sounds were faint and irregular, with

blood pressure 136/85. The abdomen was protuberant. There was a para-umbilical hernia which was reducible. The liver was palpable 6 fingers below the costal margin. The 5+ edema of his lower extremities extended to include the lower abdomen and back. The electrocardiogram (Fig. 7b) showed an auricular fibrillation with a left bundle

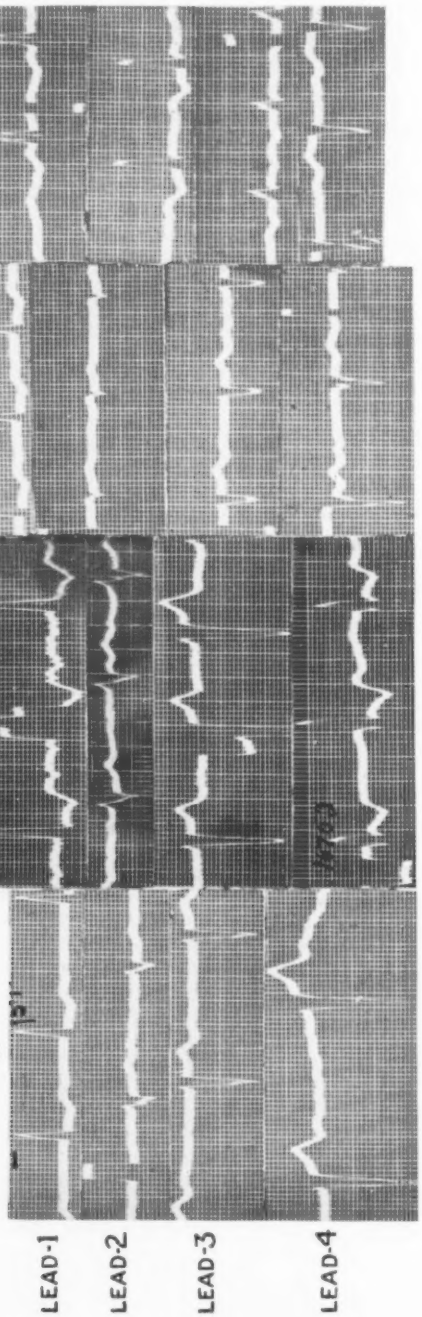

Fig. 7—Effect of 100% oxygen therapy and oxygen tent therapy in Case 3: *a*) 11 months before onset of bundle branch block; *b*) occurrence of bundle branch block during an episode of severe congestive failure; *c*) 12 hours after 100% oxygen therapy; *d*) 1 week after cessation of all oxygen therapy.

branch block. He was regarded as a critical cardiac with little hope of recovery. Following the administration of 100% oxygen through a B.L.B. mask, there was a clearing of cyanosis. After 12 hours of therapy, an electrocardiogram showed a disappearance of the bundle branch block (Fig. 7c). Because of continued orthopnea, further oxygen therapy was continued in a tent. Though the signs and symptoms of congestive heart failure receded after 9 days of adequate digitalization and daily mercurial injections, slight cyanosis became evident as soon as he was removed from the tent. He was given intermittent oxygen tent therapy for another 3 days when it was found that he no longer became cyanotic without the use of oxygen. He had improved to such a great extent that he was permitted out of bed 2 weeks after admission. In spite of repeated mercurial injections, there was a gradual fall in the blood nonprotein nitrogen from 43 mg. on admission to 30 mg. on discharge with no evidence of casts or red blood cells, though there was a constant outpouring of 2+ albumin in the urine. There was a loss of more than 25 points of edema fluid. Of particular interest was the Roentgen-ray evidence of the absorption of all the pleural fluid. Though there was no reduction in the size of the cardiac shadow, now one could visualize quite clearly the descending branch of the left coronary artery as a calcified vessel. An electrocardiogram taken a week after oxygen therapy had been discontinued still failed to show any evidence of bundle branch block (Fig. 7d). When it became evident that the cardiac failure did not recur on ambulation for 14 days, he was granted his wish to continue his convalescence among his cronies in a nursing home.

Discussion. While it is realized that the presence of bundle branch block does not influence the treatment of the causal lesion, a better understanding of the circumstances producing the abnormal electrocardiogram will do away with the nihilistic attitude of physicians regarding its therapy[5]. There have been numerous reports of the spontaneous return of bundle branch block to normal conduction, lending credence to the belief that the bundle branch block was "transient" or "paroxysmal" in nature and of little import to the subsequent health of the individual.

Though no anatomical cardiac lesion may be detected, the periods of bundle branch block are primarily due to abnormal changes in the conducting tissue and therefore should be regarded as a manifestation of heart disease. One or several physiological factors may be responsible for the appearance of the disturbed conduction. Each factor must be investigated and eliminated with whatever means are available.

Some patients may return to normal conduction with bed rest or limitation of activity[17]. Other patients may respond to diuretic therapy[16]. The most common methods of eradication of bundle branch block have been by the application of carotid sinus pressure[4,23], or the administration of acetylcholine[20]. But in all such cases, the bundle branch block returned when the cardiac mechanism resumed the critical rate that initiated the disturbance. The most rational approach to the problem is to administer oxygen by inhalation. Obviously this type of therapy will not clear up the bundle branch block in patients whose conducting tissue has been irreparably damaged by disease. However, one can conceive that such damage might be prevented by the early and prolonged use of oxygen. Such a conception is based on sound experimental work performed on dogs. Resnik[18] demonstrated that anoxemia caused changes in the intraventricular conduction of a normal heart by a direct effect on the myocardium. Furthermore, the appearance of the stage of impaired conduction was favored by the condition of the heart, the rate at which the heart beats, the degree of anoxemia and the length of time to which the heart was subjected to asphyxia. Several years earlier Barach and Woodwell[2] demonstrated the beneficial effects of oxygen inhalation in 2 cases of bundle branch block. Both

patients were cyanotic due to severe myocarditis and cardiac insufficiency. The electrocardiographic changes indicated a lesser degree of block during and following the inhalation of oxygen. The good results were attributed to an improved circulation due to the elevation of oxygen saturation of the arterial and venous blood to the normal level. Later, Baker[1] was able to eradicate the bundle branch block of a patient following 5 minutes of oxygen inhalation. In addition, during oxygen inhalation, though the cardiac rate could be increased well above the point provoking delayed conduction in all previous observations, the normal ventricular complexes prevailed. However, this type of therapy has received little, if any, support in recent years, although no actual evidence opposed to it has been presented.

Conclusions. 1. Bundle branch block can be caused by a single agent or by various combinations of anatomical, pathological or physiological factors.

2. A careful study of each case may reveal sufficient data to establish the etiological or physiological basis for the existence of the bundle branch block.

3. A case is reported in which coronary artery occlusion with faulty oxygenation of the bundle of His was the cause of the bundle branch block.

4. With adequate oxygenation by the use of 100% oxygen inhalation the bundle branch block at first was eliminated temporarily and finally eradicated completely.

5. Finally, 2 cases are reported to show that adequate oxygen inhalation may eradicate completely bundle branch block in hearts that have been severely damaged by disease.

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RUTIN THERAPY IN DIFFUSE CAPILLARY BLEEDING: INEFFECTIVENESS WHEN FRAGILITY TESTS ARE NORMAL

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Kushlan[7] reported in 1946 a detailed description of an individual with hereditary hemorrhagic telangiectasia who presented the usual course of this disease with variable amounts of bleeding from the gastrointestinal and respiratory tracts, and subsequent anemia. Treatment was basically unsatisfactory and was necessarily blood replacement either by transfusion or by increased oral iron and protein intake. He was given Rutin in a dosage of 60 to 100 mg. a day with startling therapeutic results within 24 hours after onset of this drug. A subsequent communication[8] told of the recurrence of hemorrhagic phenomena with the use of sulfadiazine to combat a urinary infection. When the sulfadiazine was discontinued and the dose of Rutin doubled, the bleeding promptly ceased.

In a 1947 editorial[2] a fairly detailed historical review of available information on hereditary hemorrhagic telangiectasia is given. Emphasis is placed on the variability of the disease manifestation. Hope is expressed that Rutin may be a specific in therapy. Schuster[13] pointed out that individual groups of dilated vessels are not permanent but vary from time to time in their number, size, and tendency to bleed, even to the point of disappearing entirely."

Kushlan's apparently has been the initial report of the use of chemotherapy in this disease. Prior to this, topical fulgeration and blood replacement have been used. Snake venom was introduced in the early 1930s for a heterogeneous group of bleeding conditions. Pecke and Rosenthal[11] reported particularly good results in the parenteral application of snake venom for hereditary hemorrhagic telangiectasia.

In an advanced instance of this disease the visible lesions present as tumor-like masses of fine capillary dilatations involving the submucosa and frequently the epithelium proper. Protruding angiomata overly, and the gross appearance is that of a mass of superficial, blood distended, venules unprotected by any epithelial covering. It seems remote that any systemic therapy could produce adequate alleviation. By contrast, the small lesions are well epithelialized and entirely nonbleeding even when on the face and repeatedly traumatized as by shaving.

The diagnosis of this disease is made on the basis of family history and clinical examination. There are two commonly used methods of evaluating capillary fragility: the Rumpel-Leede test[9,12] and the Göthlin Petechial Index[5] as modified by Griffith and Lindauer[6]. The Rumpel-Leede test is performed by inflating a blood pressure cuff 10 mm. above the diastolic pressure for 5 minutes and counting the subsequent petechiae produced 4 cm. distal to it in a 2.5 cm. square area. More than 20 petechiae in this area that persist after deflation and the disappearance of the subsequent cyanosis is considered to indicate increased "capillary fragility." The Göthlin Index is performed at infra-diastolic levels. The cuff pressure is maintained at 35 mm. of mercury for 15 minutes on each arm. The resultant petechiae production is counted with a hand lens in a 6 cm. circle in the antecubital fossa. One hour later, this is repeated bilater-

ally at 50 mm. pressure. The Index is calculated by adding twice the amount of petechiae at 35 mm. to the amount produced after 50 mm. inflation. Eight or less is considered normal. Thirteen or more indicates abnormal capillary status.

Soloff and Bello[14] have pointed out that the presence of subclinical scurvy exists in many diseased states. In their testing they precluded this by giving adequate ascorbic acid and Vitamin B Complex for a month prior to examination. They concluded that after scurvy, niacinamide deficiency, thiamin deficiency, or ariboflavinosis have been excluded, Rutin, in therapeutic dosages did not reverse to normal, patients with positive Göthlin and, or, Rumpel-Leede tests.

Prior to this, Bell, Lazarus, and Munro[1] in 1940 reported a 10.7% positive Göthlin Index in normal students, All but 2.5% of these reverted to normal with therapeutic doses of Vitamin C.

Levitt, Cholst, King and Handelsman[10] in a detailed study treated 12 diabetic patients, with both increased capillary fragility and retinal hemorrhages. They could not demonstrate any associated improvement due to Rutin therapy.

Here 5 cases in 2 families of moderately to far advanced instances of hereditary hemorrhagic telangiectasia and their response to intensive Rutin therapy are reported.

Case Reports. CASE 1. Ja. G. White male, aged 47, with clinical manifestation of hereditary hemorrhagic telangiectasia with massive epistaxes of 13 years' duration. During this period, he has had 231 (500 cc.) transfusions.

His paternal grandfather died at the age of 86 although he "bled from his nose all his life." His father died at the age of 56 with a diagnosis of pneumonia after a week of "continuous nasal bleeding." A second cousin, male, aged 56, physician, died of cardiovascular collapse subsequent to attempted nasal reconstructive surgery and massive bleeding. His brother is Case 2. He has an older sister who bleeds slightly. None of her 3 children has any bleeding tendency. An older brother, now aged 52, has never shown any bleeding tendency, nor have either of his 2 adult sons. Case 3 is a second cousin. Ja. G. has 2 daughters, aged 15 and 20. Neither have had any bleeding tendency.

His appearance is startling. There are multiple areas of telangiectasia on his face, leaving only patches of clear skin. This is most noticeable in the nasal folds and naso-labial areas. The ear lobes are particularly involved and almost translucent. The nasal mucosa is difficult to inspect because of ready bleeding. It presents as a mass of dilated venules which bleed freely at the slightest trauma. There are a few small non-elevated patches on his buccal mucous membrane and several minute ones on his gums. Those on the hair bearing area of his face are well epithelialized and have not bled even with repeated shaving. His hands and fingers have several well epithelialized small areas. The non-exposed parts of his body are essentially lesion free.

He has a vasomotor rhinitis on a pollen sensitivity basis, and epistaxis is frequently initiated by sneezing, although many episodes begin spontaneously without trauma. Epistaxis varies from daily oozing to periodic massive terrifying episodes which preclude adequate packing by the amount of blood flow. It is following these, that immediate transfusions are necessary.

His past history includes a left nephrectomy at the age of 37 for pyonephrosis. He has had repeated blood surveys in his many hospital admissions, and at no time has any blood abnormality except secondary anemia been demonstrated. His spleen has been palpable and non-tender for the past 2 years.

Prior to the initiation of Rutin therapy in October, 1946, he noticed excess bleeding from gums and frequent blood stained saliva. In addition, there were frequent episodes of blood stained tears. His Rumpel-Leede test was 16 initially. His Göthlin Index was computed at 6 . . . both within normal limits. He has been taking 20 mg. of Rutin 3 times daily for 12 months and for the past 18 months this has been increased to 50 mg. of Rutin 3 times daily. Three months after institution of therapy the petechial tests were repeated. The Rumpel-Leede test was 14. The Göthlin Index has varied from 4 to 8 on 5 different occasions at approximately 5 month intervals. Clinically, his blood-stained saliva and blood-stained tears have disappeared and have not recurred. The extent and intensity of epistaxis has varied, as it had previously, being greater in the spring of the year, at the time of greatest intensity of vasomotor rhinitis. The need for transfusions has gone along at

approximately the same tempo. Within the past month there has been repeated rectal bleeding, the origin of which cannot be demonstrated. Presumably this is on the basis of a similar lesion above the area visible to a sigmoidoscope.

Throughout these past 30 months, as in the years prior to Rutin therapy, there has been repeated electro-fulguration of his nasal mucous membrane. In addition, the patient has effectively applied silver nitrate topically. A lateral rhinotomy with total removal of the septum was advised but refused by the patient.

Case 2. Ju. G. Brother of Case 1. White male, aged 43, noticed multiple lesions on his face since mid adolescence. These present as non-elevated, well epithelialized, blue to bluish red pinhead sized lesions on his cheeks and ears. He had occasional epistaxis in childhood. Since the age of 30, he has had frequent minimal to moderate epistaxis. His nasal mucosae show extensive masses of venule and capillary dilatation although significantly less than his brother. At the age of 37 he was admitted to hospital for extensive rectal bleeding, and a diagnosis of cecal neoplasm was made. Initial transfusion was given at this time for secondary anemia. Patient refused operative intervention and subsequent evaluation showed a normal colon. Presumably he was bleeding from a telangiectatic area elsewhere in his large bowel. He has had multiple cauterizations of his nose with fair improvement so that his bleeding had decreased to the point of being a major nuisance only. With iron medication by mouth, his hemoglobin level remained in the neighborhood of 70%.

In October, 1946, a Rumpel-Leede test was interpreted as 18. His Göthlin Index at onset was 7. At that time he was started on 40 mg. of Rutin 3 times daily, which he has continued to date. Since then this has been retested at approximately 4 month intervals and has varied between 4 and 8. There has been no correlation between the Göthlin Index and the extent of bleeding. He also has vasomotor rhinitis with pollen sensitivity. Unlike his brother, who has refused pollen desensitization because of several severe bleeding episodes after pollen injection, Ju. G. has followed through with desensitization and antihistaminics with fair results. Nevertheless, bleeding in the spring of the year has been conspicuous. During the winter of 1947-48 there was repeated rectal bleeding in small amounts associated with constant small amounts of nasal bleeding. In February, 1948, he was given three 500 cc. transfusions following multiple massive epistaxes. Two months later this had to be repeated following massive bleeding during manipulation with an electrocautery. There has been no further need for transfusions. With large amounts of iron and protein by mouth his red count varies between 3.1 million and 4.2 million with a hemoglobin of 68 to 80%.

Case 3. N. G. White male, aged 71, cousin of Cases 1 and 2. This man has not at any time been incapacitated by his hereditary hemorrhagic telangiectasia. He began having slight nasal bleedings at age 40 which have continued to date. There is no associated vasomotor rhinitis and there has been no local therapy to his nose. He has his nose almost continuously lightly packed with small amounts of cotton which he feels is adequate. In contrast to the previous 2 cases, his skin is essentially clear of lesions. He has had bilateral pulmonary tuberculosis with multiple sanatorium admissions, and is now classed as bilateral far advanced, arrested.

In February, 1947, his Rumpel-Leede test was 12, and his Göthlin Index was 6. He was started on 20 mg. of Rutin, 3 times daily. Because of the expense of the medication and the lack of severity of the disease, he has taken medication irregularly. He feels that it has decreased the severity of his disease and finds satisfactory results within 48 hours after re-instituting therapy. In February, 1949, after 24 months of irregular Rutin therapy his Rumpel-Leede test was 10 and his Göthlin Index 6.

Case 4. F. M. This 24 year old white married female has been reported in detail elsewhere[3] because of untoward reaction to snake venom. Her family history includes 1 sister and 2 brothers with frequent epistaxis. They have all secured relief with snake venom. She has two sisters who have not manifested any bleeding. Her mother had severe nose bleeds and died at the age of 50 of "secondary anemia." Her maternal grandfather had bled, as had a maternal uncle. The patient gave a history of frequent nose bleeds of 6 years' duration which was diagnosed as due to multiple small telangiectasia of the hereditary type on her nasal septum. There have been no cutaneous lesions. Her menses are regular. There is a definite tendency for increased bleeding from her nose at the time of menses. She has vasomotor rhinitis and hyper-reacts to various foods, pollens, and dust allergens. Repeated hematological surveys have been entirely within normal limits.

In April, 1947, her Rumpel-Leede test was 14 and her Göthlin Index 5. She was started on 20 mg. of Rutin three times daily, which has been taken irregularly to date. The cost

of the drug and the non incapacitating illness has precluded its routine use. She also feels that it has been beneficial.

CASE 5. A. C. Brother of Case 4. He has been observed only on 2 occasions at widely separate intervals. He was seen initially in the spring of 1947 at the age of 29 with a 15 year history of frequent epistaxis, non incapacitating, and for which no specific therapy was applied. He requested examination for repeated small hemoptyses of 3 months' duration, unassociated with respiratory infection or constitutional symptoms. Physical examination was essentially negative except for several small telangiectatic areas on his cheeks which had never bled despite their being in the shaving area. A complete nose and throat survey showed extensive telangiectatic areas in the anterior nasal septum. Roentgen-ray examination of the chest at that time, and a repeat film 10 weeks later, showed normal pulmonary parenchyma. At the time of his initial examination his Rumpel-Leede test was 14 and his Göthlin Index was 6.

Rutin (50 mg. 3 times daily) was prescribed. Direct contact was lost and information through his sister was inadequate. Apparently he took Rutin irregularly. Hemoptysis continued intermittently for 6 to 8 months and has not reappeared for the past year. The tempo and extent of epistaxis is apparently unchanged.

CASE 6. E. S. White female, aged 51. She was seen here initially at the age of 49 with a request for a routine check. Her past history includes multiple "bruises" following minimal trauma "all her life." She was hospitalized in 1932 for a "nervous breakdown" preceded by a week of temperature elevation, chills and fever. The records of this illness have not been available. She was hospitalized in the latter part of 1944 for 3 weeks following 1 month of chills and daily temperature elevations. A fairly careful work-up showed no specific lesion and she was discharged as "Pyrexia of Unknown Origin" following negative results from multiple chemotherapeutic and antibiotic agents. She was rehospitalized elsewhere 2 years later with a similar history, again treated with antibiotics and discharged asymptomatic with a diagnosis of "Fever of Undetermined Etiology."

Examination here showed bilateral cystic breast disease, a moderate secondary anemia with an erythrocyte sedimentation rate of 86 mm. in 1 hour (Westergren, normal 10 to 20). A Rumpel-Leede test produced countless petechiae formation with large ecchymotic blotches. Her Göthlin Index was computed at 40 (normal 8 or less). Cevitamic acid in dosage of 50 mg. per day was prescribed. She was rechecked one month later, at which time her Göthlin Index read 42. The Rumpel-Leede was not repeated because of the initial untoward results. Physical examination was unchanged. Her erythrocyte sedimentation rate was 78 mm. in 1 hour (Westergren). After 6 months of Vitamin C therapy, physical and laboratory results were unchanged. At that time, she was placed on 50 mg. of Rutin 3 times daily. Two months later re-examination showed a Göthlin Index of 28 with an erythrocyte sedimentation rate of 84 mm. in 1 hour (Westergren). After 6 months of Rutin therapy her erythrocyte sedimentation rate had decreased to 52 mm. in 1 hour (Westergren), with a Göthlin Index of 20. At this time she volunteered the information that she bruised less easily. This remained essentially unchanged for 1 year. At that time, following 3 days of chills and temperature elevation to 106°F., she was hospitalized. Physical examination showed a questionable spleen enlargement. She had slight but definite nuchal rigidity. Lumbar puncture showed 40 to 50 red blood cells per cc., with 1 to 2 white cells per cc. There was no increase in pressure. The protein content was normal. The fluid was sterile. The entire syndrome subsided within 8 days and she was discharged essentially symptom free. She evidently had a small intra-cerebral hemorrhage with an unusual febrile result. She insists that this event was identical to the 3 other hospital admissions.

She has continued essentially well, to date. Post-traumatic bruises occasionally but infrequently arise. Her Göthlin Index on repeated examinations remains at 15, her erythrocyte sedimentation rate at 34 mm. in 1 hour (Westergren).

Discussion: Hereditary hemorrhagic telangiectasia has been a well recognized clinical entity for over 40 years. In the past few decades, with blood replacement readily available, the lives of people afflicted with this disease can be prolonged. Efforts to stem the source of blood flow have, in general, been unsatisfactory. The milder cases can be controlled, or the extent of the disease brought to the point of nuisance value only, by the use of snake venom. This apparently adequately increases blood viscocity. No instances of abnormal intravascular clotting have been reported with its use.

Topical electric or chemical fulguration to available bleeding points works well where it is applicable. Extensive epistaxis may be from points beyond the reach of the cautery tip. Gastrointestinal or deep respiratory sites of bleeding are not available for topical therapy.

A remarkable item in this disease is the spontaneous variation that occurs in the appearance of the lesions and the extent of bleeding. Because of these spontaneous variations it is hoped that medication systemically applied can adequately alter the capillary or venule permeability.

Kushlan's reported case[7] with excellent therapeutic results raised the hopes that a specific had been found. However, Goldman, Asher, and Ware[4] report 2 instances of this disease in which Rutin was used therapeutically without discernible improvement.

Five cases of hereditary hemorrhagic telangiectasia with Rutin used in adequate dosages for as long as 3 years are reported. In no instance was there diffuse increased "capillary fragility" as manifested by "positive" Rumpel-Leede or Göthlin indices. In no instance did the extent of bleeding correspond or vary with the readings of these 2 indices. No objective evidence of therapeutic efficacy was obtainable through the prolonged and adequate use of Rutin. Patients 3 and 4 thought that Rutin decreased their bleeding tendency, but the dosage was so irregular that this cannot be held valid.

In contrast, 1 instance (Case 4) is presented with diffuse capillary permeability of undetermined etiology, who had a markedly increased Rumpel-Leede and Göthlin Index. She responded to Rutin with a definite decrease in clinical bleeding phenomena and a corresponding decrease in her "capillary fragility" indices. To be noted is a parallel alteration of her erythrocyte sedimentation rate.

In no instance was sulfonamide therapy used during this observation. Its use is reported[8] to interfere with the usefulness of Rutin therapy.

Conclusion. The use of Rutin in 5 cases of hereditary hemorrhagic telangiectasia with normal capillary fragility tests, in adequate doses for 2 to 3 years, has not yielded any objective therapeutic result. By contrast 1 case of diffuse "capillary fragility" has responded satisfactorily.

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PRECIPITIN REACTION OF SERUM FROM CASES OF RHEUMATOID ARTHRITIS WITH HOMOLOGOUS CONNECTIVE TISSUE EXTRACTS

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The clinical picture of rheumatoid arthritis, in common with that of several other collagen diseases such as serum sickness, periarteritis nodosa, disseminated lupus, and rheumatic fever, presents many features such as fever, increased sedimentation rate, leukocytosis, and increased serum globulin that are ordinarily regarded as the body's reaction against chronic infection. However, no infection has been found to account for this reaction, and the fact that similar reactions are found in the case of gout, which is believed to be a purely metabolic disease, and in the case of serum sickness, where the question of infection does not enter, has led to the hypothesis that the primary disturbance in rheumatoid arthritis may be in the immunity mechanism. Nevertheless, it is still possible that this disturbance in immunity is not a primary one, and that it occurs in response to some unknown antigen not necessarily of direct infectious origin. The overall long-range clinical picture of rheumatoid arthritis is that of local inflammation ending in the absorption of certain connective tissue structures as though these were acting as a foreign body to which the host had developed immunity.

Theoretically, it is possible that an infection could render the connective tissues antigenic by adsorption of antigenic radicals, or that some abnormal metabolic change in the connective tissues could make them behave as antigens. Another possibility is that the antigenic hyaluronic acid components of certain bacteria might create antibodies which, through overlapping action, are capable of reacting with the normal hyaluronic acid component of the connective tissue system, thus setting in motion a chronic antigen-antibody reaction.

The present exploratory study was undertaken in an attempt to determine whether rheumatoid tissues might be themselves antigenic, thus evoking a chronic state of hyper-immunity, or whether the connective tissues themselves are normal, but are being attacked by abnormal immune bodies due to a primary disturbance in the immunity mechanism not necessarily related to infection.

Methods. The complement fixation reaction and precipitation reaction were selected for use in this study. Tissues surgically removed from 6 patients with typical active rheumatoid arthritis were used as the test "antigens". These consisted of typical subcutaneous rheumatoid nodules in 4 instances and material from joint structures in 2 other instances. Control "antigens" consisted of tissues removed from non-arthritic patients undergoing surgical procedure. These were, respectively:— Joint capsule, synovium and surrounding connective tissue in two instances, and lymph nodes in the two

remaining cases. One of the lymph nodes was secured during a herniorrhaphy and the other was excised as a biopsy procedure and was reported as histologically normal except for "inflammatory change". Test serum was secured from patients suffering from severe typical rheumatoid arthritis of varying degrees of activity and chronicity. In one instance only the test serum and test tissue came from the same patient. Control serum was obtained from volunteers among the resident and interne staff of Temple University Hospital all of whom gave a negative history for any connective tissue disease.

Preparation of "Antigenic" Material. Tissues were received directly from the sterile operating field, immediately placed in sterile bottles containing a solution of 0.3% phenol in saline and kept at −15° C. for 1 to 6 months until a sufficient number of specimens had been collected. At a given time the specimens were thawed and, under sterile technique, freed from fat, minced and ground with purified antigen-free sand and then washed with 0.3% phenol in saline into sterile test tubes so that the suspended tissues made approximately a 15% mixture by volume. These were agitated, refrigerated for 8 hours, agitated again, and refrigerated for 16 hours. Following this extraction period the supernatant fluid was decanted and centrifuged at 2500 RPM for 10 minutes. The layer of fluid between the sediment below and a thin meniscus of fat on the surface was pipetted off, cultured to verify sterility and kept at −15°C. until the serologic tests were to be made. On the day preceding complement fixation determinations the "antigenic" solutions were tested for anti-complementary activity and then diluted sufficiently to avoid false positive reactions.

The serum was prepared by withdrawing the blood on the same day as the test, allowing it to clot, centrifuging it and pipetting off the clear supernatant serum.

Complement fixation tests were carried out by the one fifth method of Kolmer[1] and the tests were performed in Dr. Kolmer's laboratory using this standard technique. The tests were read 10 minutes after the controls were hemolized. The precipitin tests were set up using the same antigen solutions and, when possible, serum from the same donors as in complement fixation tests. Then 0.2 cc. of serum was gently overlayed with 0.5 cc. of "antigenic" material. Preliminary readings were made at the end of 30 minutes, and a clouding at the junction of the 2 layers was interpreted as a positive test. The tubes were then incubated at 37° for 1 hour and re-read, and, after being kept in the refrigerator for 48 hours, were read for the third time. In all instances "antigenic" solutions and sera were identified only by number and the specimens were purposely randomized to avoid bias in reading.

Results. The results of 100 complement fixation tests and 100 precipitation tests are summarized in tabular form in Table 1. Reading from left to right, the vertical columns, 1 to 6 inclusive, represent the reactions of rheumatoid serum, the vertical columns, 7 to 10 inclusive, the reactions of control serum. Readings along the horizontal lines, 1 to 6 inclusive, represent the interaction of the sera with antigens from rheumatoid tissues, and 7 to 10 inclusive indicate the reactions between control antigens and sera. The vertical column 11 and the horizontal line 11 indicate saline controls. Positive complement fixation readings are represented by X and positive precipitation test by +.

It will at once be evident that out of the possible 200 reactions all except one occur between rheumatoid sera and tissue extracts of both rheumatoid and non-rheumatoid origin. In only one instance did a control serum give a feeble positive result and that was with the precipitation reaction. Out of 72 possible reactions between rheumatoid sera and rheumatoid-tissue antigens, 24 positive tests were obtained; out of 48 possible reactions between rheumatoid sera and control tissue antigens 9 positives are noted. A further analysis shows that only 9 of the total 34 positive reactions occurred with the complement fixation test and these occurred only with rheumatoid sera. Since in the case of serum 6 the next lowest dilution was anti-complementary, these particular readings are of questionable validity and, if eliminated, would leave a total of only two bona fide, positive complement fixation

TABLE 1.—REACTIONS BETWEEN SERA AND HOMOLOGOUS TISSUE EXTRACTS

		Rheumatoid Sera						*Control Sera*				
		1	2	3	4	5	6	7	8	9	10	11
Rheumatoid Tissue	1		+		+	+	X					
	2	X +					X					
	3	+				+	X					
	4	X +	+		+	+	X					
	5						X					
	6	+	+		+	+	X					
Control Tissue	7	+	+		+						±	
	8	+			+	+	X ±					
	9											
	10	±										
	11											

Positive precipitation reactions indicated by +
Positive complement fixation reactions indicated by X
Blank space indicates no reaction.

reactions. These were very feeble and of only border-line positivity. It would thus seem that in general both rheumatoid and control serum when tested against antigens extracted from both rheumatoid tissue and control tissue give essentially negative results by the complement fixation method. On the other hand there is relatively strong evidence for the power of rheumatoid sera, as opposed to control sera, to enter into a precipitation reaction with both rheumatoid and non rheumatoid homologous tissue extracts.

In the present study the sera were tested as to blood type, Wassermann reaction, anti-hyaluronidase titer, sensitized anti-sheep cell hemolysin titer and sedimentation rate without any discoverable correlation between these findings and the ability of the serum to precipitate the "antigens". Likewise there was no clear relation between the precipitation test and the duration of the disease, the sex or age of the patient, the clinical evaluation of the activity of the disease or the use of gold salt therapy.

Discussion. From these data it would appear that there exists in the blood serum of rheumatoid arthritis patients, but not in the blood serum of normal individuals, a factor capable of precipitating a fraction present in a saline extract of homologous mesenchymal tissue. It is not possible to say that this is a true antigen-antibody relationship; indeed, the fact that such weak or negative results occurred with the complement fixation tests suggests that this is not the case. The reaction may be similar to the so called "enhancing" activity suggested by Wallis[2] which causes the serum of rheumatoid arthritics to precipitate a variety of bacteria, including the hemolytic streptococcus, also to precipitate collodion particles and even form precipitates on contact with physiologic saline. Also it may be analogous to the situation in

which a patient's serum is able to agglutinate and precipitate his own erythrocytes as commonly observed in the erythrocyte sedimentation rate test, or to the phenomenon of "blood sludging". It is conceivable that this substance in rheumatoid serum which reacts with connective tissues extracts may be the circulating agent or toxin which causes the mesenchymal lesions of the disease. The fact that the rheumatoid serum reacts only a little less often with the control tissues than with rheumatoid tissues, together with the negligible number of positive complement fixations, indicates that the abnormality is in the serum and not in the connective tissues and that the latter are not acting as antigens.

Summary and Conclusion. A serologic study by means of 100 complement fixation tests and 100 precipitation tests in which serum was titrated against homologous tissue extracts is reported. Rheumatoid serum caused significant precipitation with both rheumatoid and non-rheumatoid tissue extracts, but control serum did not react significantly with either rheumatoid or non-rheumatoid tissue extracts. In only a few instances was the complement fixation test positive in either test or control groups.

We have demonstrated therefore in the serum of patients with rheumatoid arthritis, the presence of a factor capable of precipitating a fraction of a saline extract of homologous tissues. Evidence that the connective tissues of the rheumatoid patient have antigenic properties, as judged by the complement fixation reaction, is inconclusive or negative.

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COPPER THERAPY OF RHEUMATOID ARTHRITIS*

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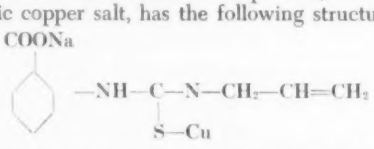
Twenty-seven patients with typical rheumatoid arthritis have been treated with an organic copper salt (Cupralene) administered intravenously during the past year and a half. This study was undertaken because of Forestier's favorable report on his experience with the drug[1,2]. In 1946, he reported 50 cases of rheumatic disease, the large majority of which were of rheumatoid arthritis, treated with the organic copper salt Cupralene with strikingly good results. The outstanding feature in his report was the total absence of any serious toxicity from the drug, with, at the same time, very marked beneficial effects on the arthritis. Because of its freedom from bad effects, it would seem to offer, if effective, an excellent addition to the armamentarium of the physician treating rheumatoid arthritis. Forestier's experience indicated that in general the early cases of rheumatoid arthritis (of a duration of less than 1 year) responded most favorably and, in the cases of longer duration, results were much less dramatic. No cases of Marie-Strümpell spondylitis showed any favorable response.

Material and Method. Cupralene, an organic copper salt, has the following structure:



The first group of 20 patients treated in this clinic with Cupralene were all instances of unquestionable, severe rheumatoid arthritis. The patients had been either resistant to gold therapy or could not tolerate it because of toxicity. In the first course of treatment, doses were used as recommended by Forestier: an initial dose of 100 mg. intravenously, followed by doses of 250 mg. given twice weekly, until a total of 4 gm. had been administered. Many of these patients for the last dose were given 500 mg. intravenously without any untoward result. A total dose of 4 gm. was considered a full course of therapy in Forestier's report. Although a few of the patients treated reported subjective improvement, in only 2 patients was this confirmed by the criteria of the American Rheumatism Association for marked improvement or remission[4]. However, all patients tolerated the total course of 4 gm. without toxicity.

In correlating the duration of the disease in the patients who were subjectively better, it was obvious that in those who had benefited most the arthritis was of short duration. Consequently, 7 patients with unquestionable rheumatoid arthritis of less than 1 year's duration were treated in addition to the original 20. The total dosage of Cupralene in this group was increased from 4 to 10 gm. Due to circumstances such as toxicity and inability of some patients to continue visiting the clinic because of progression of their disease, all patients did not receive a full course of 10 gm. (see chart), but none received less than 4 gm. In completing the course of treatment, patients originally having had 4 gm. were continued on 500 mgm. doses weekly or semi-weekly. The new patients received an initial dose of 100 mg. followed by 2 semi-weekly 250-mg. doses. Then they also were given 500-mg. doses once or twice a week.

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Results. The results obtained with the larger doses and longer course of treatment were essentially similar to those with the smaller dose, except that toxicity was definitely increased and more severe. The patients who had had the disease for longer periods (greater than 1 year) showed no significant improvement and in the group of a duration of less than 1 year the therapy was equally disappointing.

The average follow-up period in all patients treated was at least 1 year. Although Forestier did not specify any time period for his follow-up, he did indicate that most of his patients had or had not responded after a shorter period than a year.

TOXICITY. Cupralene produces, when given intravenously, certain definite reactions in addition to toxic effects discussed below. A dose as small as 100 mg. regularly causes patients to experience a taste and smell suggesting "garlic or musterole". This is constant and definite, occurring between 8 to 12 seconds after the copper salt is introduced into the blood stream. In some instances, when a small quantity of Cupralene escaped from the vein into the subcutaneous tissues, a very severe and painful cellulitis resulted. In no instance did suppuration or necrosis occur and in 3 to 10 days the reactions subsided.

Whereas during the early course of Cupralene treatment, with 100- to 250-mg. doses administered intravenously twice a week, toxicity was rare, in the later stage using 500-mg. doses intravenously once or twice a week, toxicity was the rule. Mild toxic effects included the transient appearance of microscopic pyuria and albuminuria, almost invariably asymptomatic; occasional but severe deep protopathic pain sensation in the upper arm and shoulder, occurring when the rate of injection was too rapid; and finally, 3 instances of thrombosis of the antecubital

TABLE 1.—CLINICAL DATA IN 27 CASES OF RHEUMATOID ARTHRITIS TREATED WITH CUPRALENE

		Agglutination		Gold Therapy		Cupralene				
							Sed. Rate (mm./hr.) (Westergren)			
Patient	Duration of disease	Group A hemolytic streptococcus	Sensitized sheep cell	Before copper	Reaction	Total dose (Gm.)	Before	After	Gastrointestinal symptoms	Chills and fever
1.	8 yrs.	Positive	64	no	—	5.9	53	84	—	—
2.	9½ yrs.	"	32	yes	Anemia	10.1	90	99	—	—
3.	10 yrs.	"	32	yes	—	4.5	96	70	—	—
4.	2 yrs.	"	32	yes	Rash	10.3	65	57	—	—
5.	7 mos.	Negative	32	yes	Rash	3.9	41	73	yes	yes
6.	1½ yrs.	Positive	—	yes	Rash	10.4	13	6	—	yes
7.	4 yrs.	Negative	0	no	—	3.9	70	44	yes	yes
8.	6 yrs.	Positive	128	yes	Rash	10.0	46	38	Slight nausea	—
9.	1 yr.	"	64	no	—	3.8	84	63	—	—
10.	3 mos.	Doubtful	16	yes	—	10.0	24	43	—	—
11.	13 yrs.	Positive	7128	no	—	10.2	84	36	Slight nausea	1 severe chill
12.	10–15 yrs.	"	64	no	—	10.0	40	49	Nausea	Moderate chills
13.	1½ yrs.	"	32	yes	—	11.2	90	74	Nausea	Chill
14.	5 yrs.	Negative	16	yes	—	10.0	50	28	—	—
15.	7 yrs.	Positive	64	yes	Rash	9.6	51	35	Vomiting	Chills & fever
16.	13 yrs.	"	8	yes	Rash	3.9	58	49	Vomiting	Chill
17.	14 yrs.	Negative	8	yes	Rash	10.1	47		Nausea	Mild chill
18.	3½ yrs.	Positive	8	no	—	4.5	79	91	—	—
19.	6 yrs.	"	128	yes	Rash	10.0	100	45	Nausea	—
20.	9 mos.	"	—	no	—	10.0	23	33	—	—
21.	3½ yrs.	"	128	yes	—	4.1	52	44	—	—
22.	2 yrs.	"	—	yes	—	10.3	53	30	—	—
23.	1 yr.	Doubtful	—	no	—	8.1	25	45	Nausea & vomiting. Had to stop Cu.	Severe
24.	6 mos.	Positive	64	no	—	10.0	23	34	—	—
25.	6 mos.	"	—	no	—	10.5	22	20	—	—
26.	2 mos.	"	128	no	—	3.8	47	41	—	—
27.	6–9 mos.	"	—	no	—	8.5	87	73	Severe vomiting & nausea. Had to stop.	Severe

vein. All such thromboses resolved without difficulty or evidence of embolisation.

In describing the more severe toxic reactions, in all fairness it should be pointed out that these occurred only with the 500-mg. doses which were larger than any recommended by Forestier. After the first 500-mg. dose, most patients had no reactions, but as the dosage was continued, nausea, vomiting and chills, occurring from 1 to 8 hours later, were very common. Frequently the nausea would persist for several days with marked anorexia.

Anemias of severe degree developed in some instances in startlingly short periods. For example, in 1 patient, after a reaction consisting of nausea, chills and vomiting, on the following visit 1 week later the red blood cell count and hemoglobin had dropped from a normal figure to a hemoglobin of 7 gm. and red blood cell count of 2,000,000. Although at this time there was no evidence in the blood or urine that there had been extensive hemolysis, negative stool guaiacs together with Roentgen-ray evidence of a normal gastrointestinal tract are good evidence, in conjunction with absence of a history of hemorrhage during the previous week, that severe hemolysis of red blood cells had occurred during the reaction 1 week before. At this time, 1 week after the reaction, there was no increase in serum bilirubin or in urine urobilinogen and stool and urine guaiac tests were negative. Similar but less severe anemias occurred in other patients. No changes were observed in white blood cell counts or platelets, and no immature red blood cells were observed. On discontinuing copper therapy, all symptoms of toxicity disappeared and within a month the blood counts returned to normal.

Discussion. From our observations on 27 patients, it is apparent that as a form of therapy for rheumatoid arthritis, Cupralene is of little, if any, value. Only 2 of the 27 achieved remissions from the disease and both relapsed within 6 months, while still receiving copper or having just completed a course. The only patients who responded at all in our series were 2 of less than 1 year's duration. When one considers that the percentage of remissions in the copper treated cases is no higher than that of patients with spontaneous remissions[3] it is obvious that this copper compound deserves no place in the therapy of rheumatoid arthritis.

Conclusions. Twenty-seven patients with typical rheumatoid arthritis were treated with Cupralene. Seven of these patients were in the first year of their disease.

In only 2 of these patients did a temporary remission follow the administration of copper, which in our experience is proportionate to the percent of spontaneous remissions observed with no specific treatment.

Minor toxic reactions appeared with 100- to 250-mg. weekly doses of copper. When the dose was increased to 500 mg. at one injection, anemias of varying severity followed the injection.

Cupralene in our opinion has no value in the treatment of rheumatoid arthritis.

We wish to thank Dr. Augustus Gibson, Asst. Medical Director, Merck & Co., Inc., for the supply of Cupralene.

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MULTIPLE SCLEROSIS: A CORRELATION OF ITS INCIDENCE WITH DIETARY FAT

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In a discussion of factors which influence the incidence and character of the disease multiple sclerosis, the variations in its geographic incidence deserve special consideration[1,3,4,9,14,15]. The prevailing concept that the disease is more common in northern and colder than in southern and warmer climates is based on incomplete and inadequate evidence, but the absence of a known cause of multiple sclerosis forces us to examine this evidence more closely. Superficial examination suggests that the average per capita dietary fat intake of the populations in most of those countries thought to have a high incidence of multiple sclerosis was high prior to the recent war, whereas in most other countries considered to have a low incidence of disease the fat intake was low (see the Discussion and Table 2 for further explanation of this point). This observation, if adequately corroborated, could be of considerable significance.

The recent war has furnished an opportunity to observe the effects of significant dietary changes on large populations. Some of the countries in which these changes occurred were occupied by the German Army; yet their medical services were continued without crippling interruptions or interferences, and their civilian populations remained relatively stable. Millions of people were affected, making it possible that any alteration in the disease which might result from these dietary changes would become manifest.

The present paper is an analysis of the alterations in the dietary intake of the general population, and of the changes in the incidence of multiple sclerosis which occurred in some sections of Europe before, during and since World War II. The studies were made during 1949, and the following countries were visited: Norway, Sweden, Denmark, Holland, Belgium, England, and Switzerland.

Results. 1. The Yearly Incidence of Multiple Sclerosis in Representative Hospitals in Norway, Denmark, and Holland, and the Attending Nutrition of the People of These Countries. *Norway.* The outpatient clinic of the Rikshospitalet, Oslo, Norway, takes care of all neurological clinic patients from Oslo as well as some patients from Norway in general; about half from each source. No selection of the cases is exercised. The neurological service of the Rikshospitalet has been under the direction of Professor Monrad-Krohn during the entire period of inquiry. The number of new cases of multiple sclerosis and retrobulbar neuritis which visited the *outpatient clinic* of the Rikshospitalet each year from 1937 to 1948 is shown in the left hand column of Table 1. The diets of a number of workers' families in Oslo were determined by direct measurements of the food consumed from 1942 to 1945 by Strøm[13]. This author used the pre-war (1936-38) studies of Evang and Galtung-Hansen[8], of Hoye[10], and of Storstein[12] for com-

parison. Post-war studies are being made, but are not yet available. In their stead, Government statistics for the production, export and import of certain foodstuffs have been used to indicate trends in the diet for this period, as well as for the period preceding the war.

For some years prior to World War II the whole milk and milk product milk and its products remained about the same, and the balance of exports over imports was never significant. *During this same period the production of margarine (which contained 20% to 25% of whale oil) increased about 45%.*

Almost immediately after the German invasion of Norway in April, 1940, the composition of the Norwegian diet

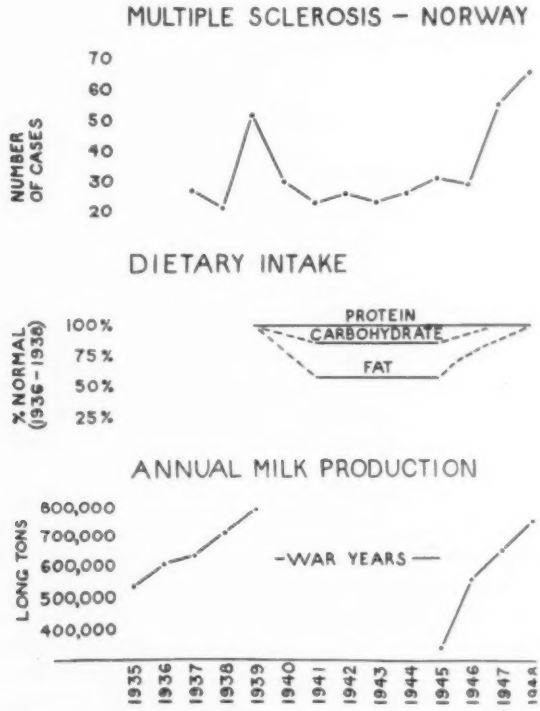

FIG. 1.—The number of cases of multiple sclerosis admitted yearly to the Rikshospitalet, Oslo; the chief changes in the diet in Oslo during the war; and the annual milk production of Norway for the pre- and post-war periods.

content of the Norwegian diet had been increasing. This is shown in Fig. 1 for the years 1935 to 1939 by the yearly whole milk production, which increased steadily each year to reach a maximum in the year 1939. During this period the export and import of changed. According to Strøm[13]* the diet of Oslo workers and their families during the war contained an average of 2849 calories per individual per day, a figure slightly lower than normal, but certainly not in the starvation range. The one known significant

* I am indebted to Professor Strøm for help in organizing and evaluating the data concerning the Norwegian diet which is described in this paper.

change in the diet of the general population was a decrease in the intake of fat to about 65% of the pre-war intake. The protein intake was about 93 gm. daily (60% animal protein), and carbohydrates about 429 gm. a day. The intake of vitamins A, B, C, and D was normal or better; the average calcium and phosphorus were satisfactory, and the iron slightly below normal. Patients with known multiple sclerosis were allowed extra milk (½ to 1 liter daily) and other foods, and it was thought that most of these patients received this extra ration.

to have been due to an improved transportation to the Rikshospitalet in Oslo as restrictions (direct and indirect) on travel ended with the capitulation of the Germans 19 months before the increase in the incidence of multiple sclerosis became apparent. However, it did attend the increase of fat in the diet which was slight in 1946, and quite marked in 1947 and 1948. This is shown in Fig. 1 by the steady and rapid increase in the yearly milk production for Norway. The importation and exportation of whole milk, powdered milk, condensed milk, butter and

TABLE 1.—YEARLY INCIDENCE OF MULTIPLE SCLEROSIS

		Denmark			
		Copenhagen			
Year	*Norway (Rikshospitalet)*	*First Admissions*	*Total Admissions*	*Invalid Insurance*	*Holland (Wilhelmina Gasthuis)*
1930		27	41	68	36
1931		11	30	72	35
1932		21	35	66	37
1933		21	37	68	28
1934		14	31	42	26
1935		24	36	69	35
1936		27	60	60	35
1937	27	19	54	65	48
1938	21	19	31	79	37
1939	52	18	44	158	32
1940	30	18	39		46
1941	23	14	37	104	31
1942	26	23	43	136	38
1943	23	22	41	121	36
1944	26	18	45	101	36
1945	31	30	42	98	32
1946	29	25	57	103	31
1947	55	17	52	104	29
1948	65	23	48		38

In Fig. 1 a positive correlation between the incidence of multiple sclerosis and the fat intake is suggested. The increase of fat in the diet prior to the war was attended in 1939 by an increase in the incidence of multiple sclerosis. During the war both the fat content of the diet and yearly incidence of multiple sclerosis were relatively low. Nearly 2 years after the war the incidence of multiple sclerosis increased to 2 and 2½ times its average war incidence. This does not appear

cheese remained fairly constant and were not significant in amounts during this period, and the consumption of margarine, which has contained about 63% whale oil since World War II, increased about 10%[17]. *The post-war consumption of margarine has been about 3 times as great as the pre-war consumption.*

Denmark. The neurological department of the Kommunehospitalet, Copenhagen (Director: Dr. Knud H. Krabbe), was used for determining

the yearly incidence of multiple sclerosis for the City of Copenhagen. Figures were obtained for 1930 to 1948. During this period the clinic has been operated by its present chief. The clinic takes all neurological patients from Copenhagen (and none from outside Copenhagen) and all patients with multiple sclerosis are admitted to the hospital. The number of cases of multiple sclerosis and retrobulbar neuritis admitted to Dr. Krabbe's clinic each year is shown in Table 1. Both the first and total admissions are listed.

The invalid insurance records, published yearly under the heading "Classification of disease by main cause of disability" in the Danish publication "Socialt Tidsskrift"[16], furnish a second source of statistics for the entirety of Denmark. These data, indicating the number of new cases of multiple sclerosis which are given sickness insurance each year are also included in Table 1.

The description of nutrition to follow was taken from 2 Danish U N F A O reports for 1947 and 1948[19] respectively, one official food study dated April 10, 1949, and other unpublished official government figures and estimates*.

During the depression, in the early 1930s, the total fat and milk consumption in Denmark was low. It was particularly low in Copenhagen and other cities. In 1936 the dietary fat began to increase, and had become much more plentiful by 1937.

The outstanding feature of the diet in urban areas (Copenhagen) during and since the war was a reduction in the fat intake due to a decreased availability of butter, margarine, lard and whole milk. The intake of fat was approximately 50% of normal from 1940 to 1944. From 1944 to 1946 this was increased to approximately 70% of normal by increasing the consumption of whole milk and cheese. Again in 1947 and 1948 the fat intake was reduced to about 50% by reducing and standardizing the butter fat in whole milk to 3% and by decreasing the lard and cheese ration. The meat supply remained unchanged during the war and its general distribution was equalized. This increased slightly the intake of animal protein of the general population to above pre-war levels. In 1947, the meat ration was reduced to 80% its war ration, and to 60% in 1948. At the same time, the consumption of fish increased. As in Norway the relative amount of carbohydrate in the diet was increased during and after the war to make up for the loss of calories from the low fat intake. This was done by increasing the ration of bread and potatoes while at the same time the ration of sugar fell to 50% of its pre-war supply. The intakes of vitamins and minerals were essentially normal and in some respects better than before World War II.

In rural districts the diet improved steadily from 1935 to 1940, and in general this improved nutrition was maintained during the war. Prior to the war the farmers sold their milk and butter, and used margarine (20% to 25% whale oil and the rest vegetable oil) for their personal use. During the war, margarine was no longer manufactured, so the rural populations consumed much of their own butter and whole milk partly of necessity and partly deliberately to lessen the export of these products to Germany. More pork meat was also consumed than before the war. This increased the intake of animal fat significantly, and at the same time the total fat intake was maintained or possibly increased.

* Dr. Erik Uhl, in charge of nutrition in the Department of Health, supplied many figures and estimates, helped to formulate, and checked the description of the Danish diet as it appears in this paper.

In Fig. 2 the yearly incidence of multiple sclerosis in Copenhagen and the yearly sickness insurance figures for all of Denmark are charted together with the changes in dietary fat for Copenhagen and rural districts. Several correlations are suggested. The first, possibly significant, increase in multiple sclerosis in Copenhagen occurred in 1936 and 1937 during the period of expanding economy and increasing fat intake after the depression. The second, possibly significant, increase in incidence of multiple sclerosis was much less pronounced and occurred in 1946 and 1947, directly after a temporary increase in the whole milk intake.

The number of patients with multiple sclerosis who received social insurance benefits annually began to increase in the year 1939 or 1940*, and continued at a much higher than prewar level until 1947 (the last year

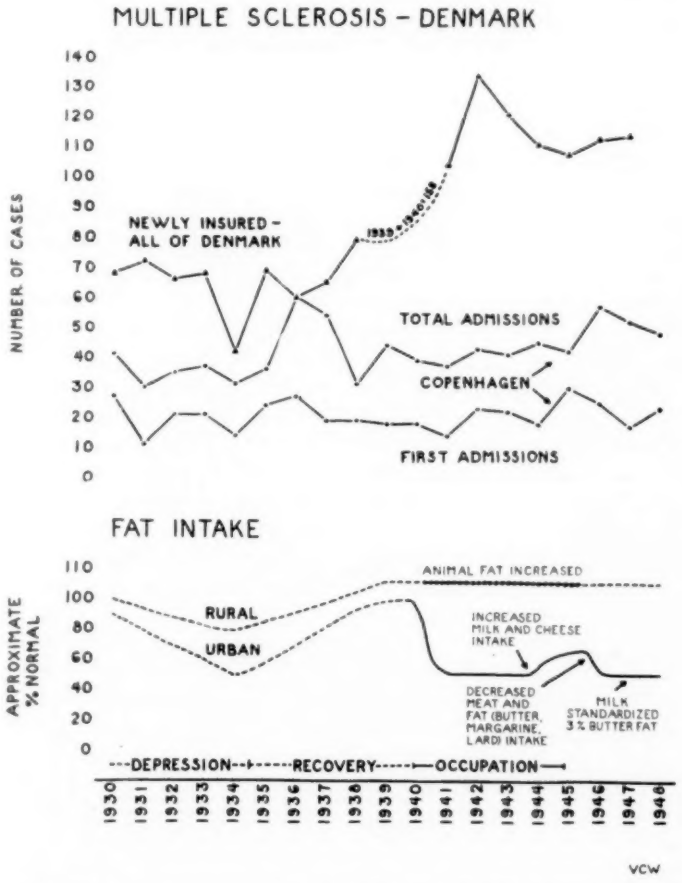

FIG. 2.—The total and first admissions of multiple sclerosis to the Kommunehospitalet, Copenhagen; number of new patients to receive social insurance yearly because of multiple sclerosis, and the rural and urban fat intake (the broken lines indicate that the figures were arrived at by estimations).

* The cases for 1939 and 1940 were recorded together. Presumably because of difficulties occasioned by the German occupation separate statistics for the two years were not issued.

recorded). This would seem to have been due to occurrences of the disease outside Copenhagen (and presumably outside other large towns as well), since no increase in the incidence of multiple sclerosis was recorded for Copenhagen. This suggests that the incidence of multiple sclerosis increased among rural populations and remained stationary among urban peoples. A change of possible significance in the diet of the rural population also occurred; whole milk, butter and pork fat increased, and margarine (vegetable fat) disappeared from the diet. It is also possible that the total fat intake increased. The low incidence of multiple sclerosis for 1934, at the "low point" in the depression, may have been due to the low dietary fat intake in all of Denmark at that time.

Amsterdam, The Netherlands. The yearly incidence of multiple sclerosis for Amsterdam was determined from the records of the Wilhelmina Gasthuis†. This hospital receives most of the cases of multiple sclerosis from Amsterdam. Since only selected cases of multiple sclerosis are admitted to the hospital, the clinic patients who did not gain admission have been added to the hospital cases in order to determine the total admissions for the neurological clinic (see Table 1).

The nutrition in Holland was extensively studied during and since the war by Dols and van Arcken[7]. In addition, figures for the various dietary substances have been published through 1947 and 1948 by the Ministry of Agriculture, Fisheries and Food, to which Professor Dols is State Advisor on Nutrition**. On October 14, 1939, rationing was started in the Netherlands, and from April 26, 1941, when potatoes were rationed, practically the entire diet was under control. By the end of the year 1943 the daily calorie intake had fallen to about 70% of normal (3000 calories daily being chosen arbitrarily for a normal adult intake). The amount of carbohydrates increased, whereas that of proteins and especially fats decreased. From the beginning of 1944 the calorie intake could not be maintained and dropped rapidly to reach its lowest point in January, 1945 (1000 to 1200 calories daily for adults 18 years and older, and as low as 600 to 800 calories for some), and remained at this level until the capitulation early in May, 1945. During the latter half of 1944 and the first 6 months of 1945, starvation was general throughout the Netherlands, and caused frequent deaths. In general the reduction of calories was due to a gradual reduction in all food factors so that carbohydrates, fats, and proteins were all greatly deficient in the diet. Early in 1945 the average carbohydrate intake was about 120 gm., proteins about 20 gm., and fat 10 gm. In the cities the black market was not an important factor, and the nutrition was better in the country than in the city. In the Netherlands, as in Norway, all chronically ill patients received additional rations. These were variable but usually included milk, meat, cheese and rice.

Following the liberation of Holland the calorie content of the diet rose immediately to about 2300 calories a day. All factors increased together: the carbohydrate to about 325 gm. daily, proteins to 80 gm., and fat to about 70 gm. The fat intake then fell to 61.1 gm. in 1946, 62.2 gm. in 1947, and 66.2 gm. during the first half of 1948. The

† Professor Biemond has been chief of the neurological service since World War II. Prior to this Professor Brouwer was chief from before the year 1930. Before becoming chief himself, Professor Biemond was Professor Brouwer's first assistant.

** I am indebted to Professor Dols for help in evaluating, formulating, and checking the information about the Dutch diet which appears in this paper.

calories through these years remained at 2400 to 2500. During the entire war and post-war period the intake of vitamins in the Netherlands was supplemented by vitamin concentrates wherever possible, and evidences of deficiency diseases were minimal. The mineral intake was generally low because of such low food intakes.

It is of interest that the dietary changes in the Netherlands during the war differed in several respects from those in Norway and Denmark. In the Netherlands there was a gradual reduction in all food factors (particularly in fat) with resultant starvation, whereas in Norway and Denmark only the deficiency in fat was significant.

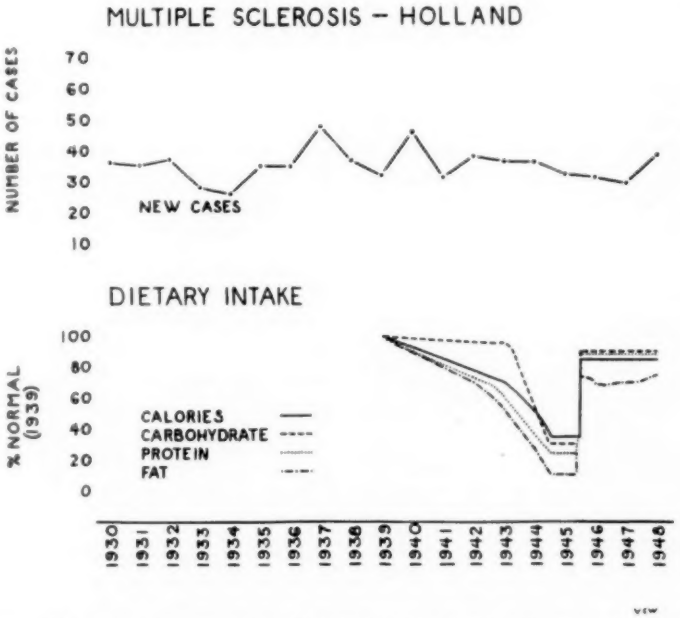

FIG. 3.—The number of new cases of multiple sclerosis admitted to the Wilhelmina Gasthuis each year and the chief dietary changes that occurred during the war.

In Fig. 3 the number of cases of multiple sclerosis seen at the Wilhelmina Gasthuis each year and the nutritional changes that occurred during and since the war are represented diagrammatically. There appear to be several trends. The incidence of multiple sclerosis seemed to be low during the depression years of 1933 and 1934, and somewhat higher during the years of expanding economy, 1937-1940, a phenomenon also suggested by the data collected in Denmark. From 1942 to 1947 there seemed to be a steady downward trend in the incidence of multiple sclerosis. No post-war increase is yet definite, which may be of significance because the fat intake has remained low while the protein and carbohydrate intakes have climbed to normal levels. If this observation is correct, it would suggest that the recovery from starvation may have little effect on the incidence of multiple sclerosis, provided the intake of fat is not allowed to increase as fast as the other factors in the diet.

2. THE OBSERVATIONS TO FOLLOW SUGGEST THAT ABRUPT CHANGES IN THE DIET MAY BE ATTENDED OR FOLLOWED

BY THE DEVELOPMENT OF UNEXPECTED CASES OF MULTIPLE SCLEROSIS. Between 1942 and 1949, approximately 5000 Jewish refugees, mostly from Vienna, Austria, were registered in the Zurich area of Switzerland by the Jewish refugee organization. Eight cases of multiple sclerosis were observed to develop among these refugees after they had arrived in Switzerland, and these cases were under observation at the University Neurological Clinic. It was known that there were other cases of multiple sclerosis among this group of refugees, as the years 1946-1948 and 1942 and 1943 were not surveyed. However, a known minimum incidence of 16 per 10,000 cases of multiple sclerosis occurred among these displaced persons*, which is at least double the highest incidence recorded in Switzerland in 1918 to 1922 (see Ackermann[1]), and at least triple the highest incidence recorded in Denmark by Gram[9].

It was thought by several observers that the main change in the diet of these refugees upon coming to Switzerland had been an increase in their animal fat intake. This is also suggested by food estimates published in the F A O publication for 1948[18], (pp. 102 to 105), which shows that the consumption of fat per person was greater in Switzerland than in Austria during the 1934-38 and 1946-47 periods.

A similar observation relative to incidence of multiple sclerosis was made by Professor Mogens Fog** among Danish repatriated prisoners. Among a group of 10,000 prisoners previously held by the Germans, 5 developed multiple sclerosis after their return to Denmark. No cases of multiple sclerosis had developed among these 10,000 men while held in German concentration camps. The severe starvation marked particularly by fat deprivation that occurred in the German concentration camps is well known. The diet of these repatriated Danes changed from one of starvation to one considered adequate, and in which an increase in fat was particularly evident.

Brickner and Brill[2] noted that exacerbations of disease were apt to occur after drastic changes in the food intake. In 2 instances this occurred when the food intake was decreased, but usually (10 cases) it was observed to occur after the reduction in diet had terminated and the food intake was increasing again. No attempt was made to correlate these exacerbations with changes in the fat intake.

3. THE NUTRITION RELATIVE TO KNOWN GEOGRAPHIC DIFFERENCES IN THE INCIDENCE OF MULTIPLE SCLEROSIS IN SWITZERLAND. The Swiss Confederation Health Service determined the relative frequency of the disease multiple sclerosis throughout Switzerland for the years 1918 to 1922. This work was performed by a commission headed by Professor Robert Bing (see Ackermann[1]). A total of 891 cases of multiple sclerosis from a population of nearly 4 million were reported, an overall incidence of 2.2 cases per 10,000 population. In the German speaking provinces in Northern Switzerland the incidence of the disease was highest, averaging 4 to 7 cases per 10,000 population. In the Italian speaking area (Tessin) in southern Switzerland the incidence of multiple sclerosis was less than 1 per 10,000, and in large areas no cases were reported. In the French speaking parts of Switzerland, the incidence of the disease varied from 1 to 3 per 10,000 population.

An analysis of the nutrition of Ger-

* Dr. Katzenstein of Zurich, Switzerland first suggested to the author that a high incidence of multiple sclerosis had developed among these refugees.

** Personal communication.

man and French speaking Swiss soldiers during the war (Demole[5]) indicates that the French speaking soldiers consumed significantly less fat and more carbohydrate than the Germans. Private communication with Dr. Demole amplified and confirmed this. He (and other nutritionists) also stated that the Italian speaking Swiss consumed a diet containing very little fat, a diet very similar to that consumed by the Italians themselves; and that the diet of the German speaking Swiss contained more fat than consumed by either the Italian or French speaking Swiss. Thus it would appear that among the German, French, and Italian speaking Swiss the incidence of multiple sclerosis may correlate directly in some way with the fat content of the diet.

Discussion. The data here presented suggest that the incidence of multiple sclerosis may be related directly to the amount of fat in the diet. It is impossible to evaluate all the known and unknown factors that have influenced these data, and their limitations are so obvious that special consideration of them will not be attempted. In partial defense of the incidence figures for multiple sclerosis, the following points will be emphasized. As already mentioned, the hospitals in Norway, Denmark, and Holland were not significantly interfered with during the war, and there were no reasons to suspect that during the period of inquiry the diagnostic criteria had changed. Since the hospitals continued to serve the same geographic areas, and the populations remained relatively stable, it is not unlikely that fluctuations in the number of admissions of multiple sclerosis indicated changes either in the frequency or severity of the disease. Personal economic considerations should have exerted a minimum of influence, as medicine and particularly hospitalization is socialized in Norway and Denmark and as in the Netherlands the hospital under consideration is a community institution and takes care of patients regardless of their ability to pay.

The geographic variations in incidence of multiple sclerosis in Switzerland (Ackermann[1]) have already been mentioned. Similar differences have been reported for the United States (Ulett[14]). Other studies in Denmark (Gram[9]) have also shown geographic differences and demonstrated that in Denmark the disease was more frequent among farmers (51 per 100,000) than city dwellers (37 per 100,000). Other estimates of the incidence of the disease have been made from hospital admission data, and for these details the reader is referred to Wilson[15], and to Bumke and Foerster[3]. Generally, it is agreed that the disease has a relatively high frequency in the northern part of the United States, Canada, the British Isles, Norway, Sweden, Denmark, the Netherlands, Germany and Switzerland, and that the incidence is low in the southern part of the United States, Carribean area, in most countries bordering on the Mediterranean Sea, South Africa (Dean[4]), Brazil, Hawaiian Islands, Japan and China. It should be noted that the incidence is high in higher income areas and generally low in the lower income areas. Among other variables, medical care is better and the recognition of the disease more accurate in the former group of countries. Insofar as it is possible to determine[18], however, the nutrition in those countries with a low incidence of the disease is low in fats and in countries in which the incidence is high the diet is relatively high in fats (see Table 2).

It is of some interest that multiple

TABLE 2.—DAILY FAT INTAKE IN COUNTRIES OF DIFFERING INCIDENCE OF MULTIPLE SCLEROSIS

Countries of probably high incidence of multiple sclerosis	*Daily fat intake*	*Countries of probably low incidence of multiple sclerosis*	*Daily fat intake*
Canada	118.3	Cuba	48.6
British Isles	122.5	Italy	60.0
Norway	118.0	South Africa	49.9
Denmark	150.8	China	40.1
Sweden	116.0	Japan	24.5
Netherlands	114.7	Rumania	52.7
Germany	111.4	Turkey	46.8
Switzerland	104.7	Brazil	51.7

All figures for fat indicate daily intake in gm. per person for the period 1934–1938. The United States and France are not included in the table as the incidence of multiple sclerosis varies considerably in different parts of these countries and fat studies are available only for the entire country. Although this is true also of Switzerland, the majority of the Swiss population live in the area of high incidence of the disease.

sclerosis was not observed among prisoners of war by Spillane[11], Denny-Brown[6], and others, although these observers were interested in neurological disorders, many vitamin deficiency syndromes were observed, and the prisoners were of an age commonly afflicted with the disease. One of the striking features of the diets of these prisoners was its very low fat content*.

Summary. In an epidemiologic study of multiple sclerosis in Europe, changes in the nutrition before, during, and since the war have been correlated with the yearly incidence of the disease during this same period. These data, plus other collected observations, suggest that possibly the incidence of the disease in entire populations may be related directly to the dietary fat. It seems clear from the observations presented in this paper, as well as from unreported clinical studies, that a high fat diet is not the cause of multiple sclerosis even though it may contribute to a high incidence of the disease by accelerating it in susceptible individuals.

* On the basis of the observations just presented the author is now treating cases of multiple sclerosis with a low fat diet (30 gm. of fat daily). These studies have been in progress for about 1½ years, a period too short to be conclusive.

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AN EFFECT OF VITAMIN B_{12} ON PAIN IN NUTRITIONAL NEUROPATHY*

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The purpose of this paper is to record some changes in the symptoms and signs observed after an intramuscular injection of 15 gamma of Vitamin B_{12} concentrate† in 3 malnourished persons affected by painful peripheral neuropathy. No such response was observed following an identical procedure in 25 patients with pain caused by a miscellaneous group of neurologic disturbances not commonly ascribed to disordered or deficient nutrition. It could not be found that Vitamin B_{12} exerted any analgesic effect in normal persons.

A brief scrutiny of the enigma of nutritional neuropathies provides a useful point of departure for these observations. It would be a matter for surprise if the integrity of function and structure of human sensory or motor nerves were independent of any of the 50 odd essential nutrients. Nevertheless, there is no consensus regarding the pathogenesis of the so-called nutritional neuropathies, the identity of specific deficient factors or the relationship of depletion of such factors to those toxic, infectious or metabolic disorders in which peripheral nerves may have a disturbed function. We do not know whether interference with a single enzyme system underlies all neuropathies which have basic similarity in signs and symptoms, or whether a variety of disturbances, implicating diverse metabolic systems, produces a fairly stereotyped pattern of results because highly specialized peripheral nerves have only a narrow range of function. We have no good clue as to why sensory rather than motor nerves are more liable to injury from dietary depletions. Indeed, though there are shrewd guesses, we do not know with assurance why in nutritional neuropathies the nerves of the lower extremity are likely to suffer earlier, and to a greater extent than those of the arms, or why feet usually are affected sooner and more severely than the knees or thighs.

The finality of the statements of textbook and journal vanishes when one encounters an individualized problem in the person of a sick patient and we must admit that the specific factors concerned in the pathogenesis of nutritional neuropathy have never been defined with clarity. The precise relationship between Oriental beriberi, American alcoholic neuritis, the neuropathies of prison camps of World War II, and such conditions as dia-

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† Kindly supplied by E. R. Squibb & Sons.

betic neuropathy or the neurologic disorders of pernicious anemia is unknown. The role of thiamine in nutritional neuropathies is the subject of a startling lack of concord among experts[1,8,10,12]. No such unanimity of uncertainty exists about Vitamin D and rickets, Vitamin C and scurvy, or even the major part nicotinic acid and its strange running mate tryptophane have in relation to pellagra[7,11]. There is agreement regarding the part thiamine deprivation plays in Oriental beriberi, though data upon which agreement was reached are almost scandalously wanting in control.

Much of the recorded medical writing has emanated from those whose enthusiasm for exploiting a newly available vitamin far outweighs their training in clinical neurology or even clinical observation. We do not know what constitutes a satisfactory control, in terms of another subject or a patient standardized to serve as his own control. Against our massive ignorance of the natural evolution of such disorders this produces a state bordering upon chaos, and it is a special subject for concern when so much of the evaluation lies in the realm of the subjective[2]. It should not be forgotten that the effect of a particular nutrient administered to a depleted subject may be one or several removes from an immediate result of making good a deficiency as for instance when administration of substance A facilitates the absorption of substance B, or when C stimulates the manufacture of D or when E inhibits the formation of F or when G is transformed into H, and so on.

With reference to the curiously miscellaneous family of the B-complex vitamins, chemists, bacteriologists and students of animal nutrition have advanced so rapidly that we have a plethora of compounds, all presumably essential for the proper function of every cell in man's metabolic machinery, but for many factors we recognize no specific clinical disorder caused by a single specific deficiency. Indeed this spate of vitamins and paucity of diseases is embarrassing to the conscientious physician who hears the repeated theme of the siren song of vitamin panacea on every hand. Perhaps there is no region where early misplaced confidence in therapy has exceeded that in the field of the nutritional neuropathies. Many discarded vitamins, the specifics of a few years past, litter the therapeutic arena in a kind of parody in obverse upon the crutches at the Shrine at Lourdes. Therefore, we must use more than customary caution in interpreting the results of the studies we report now. They are brought forward as unfinished observations because patients with nutritional neuropathies are seen so rarely in this hospital that a statistically valid series might take years to collect.

While the analogy between the peripheral neuritis associated with malnutrition or chronic alcoholism and the combined sclerosis of pernicious anemia is not very close, peripheral neuritis may occur in pernicious anemia[5]. The neurologic changes in pernicious anemia improve after therapy with Vitamin B_{12}[3]. With this in mind and because therapy with various members of the B-complex for peripheral neuritis had been unsatisfactory, we were led to try Vitamin B_{12} in treating a patient who had signs of peripheral neuritis and complained of the pains in the legs.

Since much of the controversy concerning the so-called nutritional neuropathy hinges upon thiamine, it seemed expedient to control this factor by providing a diet low in this substance during the preliminary period of observation. Such a diet, containing 200 gamma of thiamine, devised for other purposes by Daum

et al.[4] was employed. We do not know all the factors which require standardization, nor can we manage all we believe to be important. At the very least we should observe the patient to establish stabilized reactions during a period of bed rest on a diet poor or lacking in the factors which might be expected to influence favorably the neurologic state. Two of the 3 patients here reported were kept on such a diet at bed rest for 1 week. The third, not under our immediate supervision, was given the test substance without any control period, but the results were of sufficient interest to record.

This report concerns 3 persons given an intramuscular injection of 15 gamma of Vitamin B_{12} concentrate and the subsequent improvement in their painful neuropathy. In no sense should it be construed as a claim that this compound may have therapeutic virtue in other similar cases. The observed effects were startling to the skeptical observers and for this reason are put on record herewith.

Case Reports. CASE 1. A 43 year old white accountant, chronically addicted to alcohol for years, was admitted because of paresthesias of his legs and feet of 8 weeks' duration and pain which prevented walking. He was chronically ill but without sign of pellagra or cirrhosis. The blood pressure was 165/105 and his heart was slightly large. Both feet were sweating excessively and were acutely painful spontaneously and to touch. The calves were tender and atrophic. Tendon reflexes were hypoactive. Decreased touch and vibratory sense existed in the legs and feet. Gait was unsteady but the Romberg was negative. Significant laboratory findings were a hemoglobin of 10 gm. and a red cell count of 3.9 million. No improvement occurred during 7 days on a control Vitamin B poor diet. On the 7th day he was given an injection of 1 cc. normal saline intramuscularly without apparent effect. Next morning he was given a similar injection containing 15 gamma of Vitamin B_{12}. Within a half hour all spontaneous pain had vanished but a feeling of numbness remained. Neurologic examination was unchanged except that pain and tenderness could not be induced. He could walk naturally. Pain recurred during the following night but was not present on awakening in the morning. There was a partial return of pain for the next 3 days. A saline placebo failed to help but 15 gamma of B_{12} again brought relief, though not so dramatically as initially. After 2 weeks of observation on the control diet, he was given a good diet with yeast, B complex tablets, riboflavin and niacin; and slow improvement continued during the next month. He was discharged then with no residual indication of neuritis.

CASE 2. A 17 year old schoolgirl was completely disabled by pain, weakness and numbness of all extremities following a siege of persisting nausea and vomiting that began 11 weeks before hospitalization without demonstrated psychic or somatic cause. The neuropathy began following treatment with intravenous dextrose. She had the pigmentation of pellagra, absent tendon reflexes, absent pallesthesia and position sense in legs and arms, tender skin and muscles and generalized weakness. No abnormal reflex was found. She had anemia, leukopenia and was later found to have a slightly elevated level of arsenic in the urine, for which there was no known cause. Similar control diet for a week and a saline placebo were attended by no improvement. Fifteen gamma of Vitamin B_{12} induced the same rapid relief of pain within 45 minutes, with some recurrence next day and less relief after subsequent injections of the same quantity. With improved diet, vitamins and physiotherapy she made further gradual improvement for 10 weeks.

CASE 3. A 58 year old blacksmith, a man with mild diabetes, addicted to alcohol and a poor diet, had painful neuritis of the legs and feet which had slowly grown worse for 5 years. It was thought that the neuritis was on the basis of alcoholism. He had mild cirrhosis or fatty liver. Codeine and aspirin had been necessary to control the pain and permit sleep. Without dietary control or placebo, 15 gamma of B_{12} were given intramuscularly, the pain ceased within 1 hour and he needed no further drugs for pain during the ensuing 2 weeks of hospitalization.

Discussion. Three patients with painful nutritional "neuritis" were relieved promptly after intramuscular injection of 15 gamma of Vitamin B_{12}. The timing made a spontaneous effect unlikely. Placebos were of no help in 2 cases. Because the response was so rapid, the effect appears to be direct

and not a response to enhanced alimentary absorption. This indicates healing of a metabolic or chemical lesion, not a morphologic one.

Because of the possibility that we had a pharmacologic effect of sedation or an analgesia, we made similar injections of B_{12} in patients with poliomyelitis, 4 with rheumatoid arthritis, 2 diabetics, 2 with multiple sclerosis, 2 with brachial neuritis, and 1 each with tabes dorsalis, trigeminal neuralgia, ruptured intervertebral disk, Korsakoff's psychosis and monocytic leukemia. These patients all had severe pain, presumably not on a nutritional basis. None experienced any consistent improvement with injection of Vitamin B_{12} or of normal salt solution.

In a study with the Hardy-Wolff pain inducing radiometer, there was no change in pain threshold in 2 well-trained subjects following intramuscular injection of Vitamin B_{12}[6]. Therefore we concluded that the results were not an effect of analgesia.

There has been no indication that permanent therapy is needed, though we have not studied effects on motor nerves over prolonged periods, thus differing from the relations prevailing in pernicious anemia. The relief of sign or symptom with a vitamin provides scant insight into the mechanisms involved. It might well be that some metabolic bridge or by-pass was opened and the relief of the clinical trouble resulted from something other than correction of an initiating depletion. We are all aware of the limited regenerative capacity of dead or moribund nerves. It is possible that the observed improvement in neuronal function resulted from enhanced blood flow through the nutrient arteries of nerves. We have no evidence that blood flow increased in the skin during the period when pain was being relieved. What relation our observations have to ribose-nucleic acid[9] and its role in the metabolism of cell and nucleus it would be premature to guess.

Summary. We injected 15 gamma of Vitamin B_{12} concentrate intramuscularly into 3 patients with painful nutritional neuropathy, which promptly improved. Further study is needed to explain the mechanism or possible significance of these observations.

Addendum. We have had another patient in whom similar improvement followed injection of 6 gamma but not 3 gamma of B_{12}, and 1 moribund patient who got no response to 30 gamma of B_{12}.

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INTRADERMAL TESTS IN THE DIAGNOSIS OF CERTAIN INFECTIOUS DISEASES

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THE responses of the skin to the introduction of various preparations of organisms, their toxins, or other breakdown products has been fruitful from the beginnings of modern medicine in the effort to detect disease. In this connection one need only recall the names of Jenner, Koch, von Pirquet, Schick, the Dicks, and Frei from among the many who have used the skin in the studies which have added so much to our present-day knowledge of immunity and the diagnosis of infection. It is our purpose here to discuss the skin responses which have been developed for the diagnosis of certain infections, giving particular emphasis to intradermal tests. The common bacterial infections (staphylococcus and streptococcus) have not been included. In addition, except incidentally, no attempt to delineate the probable immunological significance of the results of cutaneous tests will be made. Among the recent sources of information on various aspects of this subject are the papers of Kane[146], Kligman and DeLamater[154], Urbach and Gottlieb[254], and Sulzberger[245].

FACTORS AFFECTING THE RESULTS OF SKIN TESTS. Before discussing the tests for the individual infections and infestations it is necessary that the factors affecting the development of these responses be clearly understood. It is possible that many of the disagreements to be found in the literature in evaluation may be reconciled by attention to the factors about to be enumerated.

1. *Character of the Disease.* In the first place, there are certain characteristics of the disease itself which modify the outcome of the tests. There are

some diseases for which no potent skin-test antigen has been elaborated (such as torulosis[153]), or the disease may be caused by organisms or species of low antigenicity.

2. *Group Specificity.* On the other hand, material for skin-testing made from the organism or products of one disease may give reactions to other members of the same or related groups of organisms. Thus, the test for lymphogranuloma venereum may yield positive reactions in patients with psittacosis. This is especially true in antigens (animal protein or excrement) for the animal parasitic diseases, where the skin-test will merely indicate the group (such as Nematode) rather than the specific disease, e.g., ascaris infestation (see section on Cross Reactions below).

3. *Stage of the Disease.* There is always a lag phase in the development of dermal reactivity following initial infection. For this reason the skin-test is seldom of value early in first infection with any acute disease and tends, with few exceptions, to be of more importance in the diagnosis of the well established chronic infection. Thus during the earlier period of manifest disease the skin-test will yield negative results. For example, Bloch[26] found that the trichophytin reaction appeared 7 to 8 days after infection with the fungus. Peck[201,202] found positive reactions in animals days after experimental reproduction of tinea pedis with a downy type of *T. gypseum.* It requires more time in the chronic diseases which have longer incubation periods (3 weeks to 3 months in tuberculosis). Also the reaction may become negative during healing or in the terminal stage of the disease.

4. *Persistence of the Reaction after Subsidence of the Infection.* Once the test has become positive, however, it may persist for many years after the infection has subsided (29 years or more). This is frequently the case in deep fungus infections, tuberculosis, leishmaniasis and lymphogranuloma venereum. This means, therefore, that a positive test does not necessarily bear any relationship to active infection.

5. *Fluctuations in the Test Result.* In addition, there may be fluctuations in the reaction periodically, becoming positive or negative in alteration. In some instances, however, recurrence of the positive reaction may indicate relapse.

6. *Repeated Testing May Change Sensitivity.* Furthermore, repeated testing may yield a changed reaction so that tuberculin type sensitivity may decrease. In animals, however, various studies[79,133a,b] have shown that simultaneous and repeated intradermal injections of 0.1 ml. of various dilutions of histoplasm, blastomycin, and other fungus antigens may sensitize normal guinea pigs.

7. *Test Site May Affect Results.* The cutaneous reaction may vary with the skin site at which it is performed, but since most tests are made at the same sites this is of minor importance. Leiber[160] in his attempt to prove that antihistaminics reduce tuberculous allergy, showed that tuberculin tests should be repeated as far from the active focus as possible and on the same side.

8. *Effect of Pregnancy and Disease.* There may be a temporary depression of specific sensitivity during pregnancy or activity of another disease (such as decrease in reactivity to tuberculin during influenza, undulant fever and measles). There may be false negative reactions during hypothyroidism and cachexia. This is probably the result of alteration in the response of the cutaneous capillaries. Acne vulgaris apparently makes a patient resist tuberculosis[125,170,240], but this may be merely a matter of age. Not only does critical illness depress skin sensitivity to various antigens (tuberculin and histoplasmin), but this depressing effect be-

comes more marked with advancing age[104].

9. *Degree of Sensitivity of the Original Test.* There appears to be a definite relationship between the frequency of reversal of some reactions (tuberculin) and the degree of sensitivity exhibited by the patient on his original test.

10. *False Positive Reactions.* Although positive reactions occur in patients who have no history of infection nor signs of the disease being tested for (asymptomatic infection) the question of pseudo- or false positive reactions is not to be ignored. These false reactions, curiously, occur more frequently to intradermal tests than to patch-tests using antigens to the same disease[259b]. The pseudo-reactions, however, occur more frequently in known allergic individuals and they fade rapidly. The problem of false reactions is further complicated by the fact that in certain geographic locations the diagnosis of inapparent infections of healed disease is of utmost importance (histoplasmosis) making the reliability of the intradermal tests a *sine qua non* to effective epidemiologic study of certain infections.

11. *Incidence of the Infection in the Population Group.* Numerous studies have indicated that there are more positive reactions in cases of certain organisms or their congeners which are widely present in the population. This is certainly true with monilia (oidiomycin test), where nearly 100% of those tested yield positive reactions. Palmer[194] in 1946 observed that geography appears to be a significant determining factor in the prevalence of positive histoplasmin reactors which exist preponderantly in the eastern central part of the United States. The frequency of positive reactors, in general, decreases with increasing distance from this area. Negative tests are the rule in persons who have had no contact with certain of the diseases. Sexton, Ewan and Payne[230] studied a group of 356 adults of the Pribilof Islands who had probably never been in the areas where coccidiosis and histoplasmosis exist. These individuals yielded frequent strongly positive tuberculin reactions, but there were no positive results from coccidioidin and only one to histoplasmin. A few white controls reacted to coccidioidin but none to histoplasmin.

12. *Age.* The age of the individuals in the group studied with the intradermal tests for various infections is also a factor in the evaluation of the over-all results, particularly if repeated exposure of the population to the disease is a possibility. Gillard and Lecocq[108] in a study involving 7500 children between the ages of 4 and 20 years with positive reactions to tuberculin found that the cutaneous reaction became negative spontaneously depending on age. Pascher, Sulzberger and Wiener[198] showed for tuberculin sensitivity (Mantoux) that the number of positive reactions parallel the known infection incidence by age. In the case of skin reactions to toxoplasmic antigen in people of different ages without known history of infection, Feldman and Sabin[87] observed a progressive increase in positive reactions with increasing age. The effect of critical illness and age on sensitivity to skin-tests with certain antigens has been mentioned above. The age incidence of positive reactions also varies with the individual diseases; for example, Furcolow, High and Allen[105] noted that manifest histoplasmin sensitivity develops at an earlier age than does tuberculin sensitivity.

In endemic infections where skin sensitivity tends to persist, the prevalence of positive tests in the population seems to increase with advancing age. In instances where skin sensitivity may be lost with time, age may have a definite bearing on positive tests, particularly if the disease tends to be most preva-

lent during any particular period in the life span (that is, in childhood).

13. *Sex and Race.* Sex and race also play a role in the incidence of positive reactions to cutaneous tests. In the case of tuberculin and histoplasmin, for example, Furcolow, High and Allen[105] observed that there were more positive histoplasmin reactions among white than among Negroes, and that there were more positives among males than females (confirmed by Prior and Allen[207]). The percentage of positive tuberculin reactions is 3 times higher among Negroes than white and there is but little difference in the 2 sexes and lifetime and non-lifetime residents. Although these exhibit themselves as racial characteristics they may be on a socio-economic and intellectual basis. The reactions of children in the same family have been studied with histoplasmin by Ferebee and Furcolow[88]. They noted that there is a similarity in the histoplasmin sensitivity between children in the same family; that this similarity grows less marked as the children grow older; that the closeness in age of siblings influences the degree of similarity; that after the similarity between siblings produced by the known factors affecting the frequency of histoplasmin reactors (geography, sex, age and race) has been eliminated, there is still present some factor which makes siblings of a reactor more apt to react to histoplasmin than siblings of a non-reactor. Further study of this problem may reveal other factors causing variations in levels of histoplasmin sensitivity. Constitution type, as suggested by Bleckmann[25] in his study of tuberculin, may play an important role in individual sensitivity to various infection antigens.

14. *Therapy.* The effect of therapy on the behavior of the intradermal reactions is difficult to evaluate since there may be spontaneous changes incident to healing of the disease itself. A good example of what is involved in this problem is reported by Sagher[221a]. He observed activation of an originally negative intracutaneous Leishmania-vaccine reaction in a patient with recurrent leishmaniasis after Grenz ray therapy had effected cure. Antihistaminic drugs may depress the reactivity of a patient to a particular antigen. Cortisone and ACTH may also depress the reaction to tuberculin and other bacterial antigens[250a].

15. *Technical Details.* A variety of technical details enters into the consideration of the outcome of cutaneous tests. Among these are the source of the antigenic material (as in the "Frei" test for lymphogranuloma venereum, human vs. mouse brain vs. embryonated egg culture virus, or crude vs. purified antigen) variability of different lots of antigens; concentration of antigens; standardization of dosage; time of reading the test (question of delayed reactions); controls and miscellaneous factors.

The intradermal test of lymphogranuloma venereum is an example of how increase in knowledge about the causative organism of a disease makes it possible to produce an antigen which is better suited for diagnostic purposes. In 1925 when Frei introduced his cutaneous test, his antigen was essentially a mixture of a small amount of the specific virus with a large amount of pus and other contaminating organisms. In spite of the uncertain nature of the composition of the antigen, it served the most useful purpose of collating a number of clinical phenomena into a uniform clinical whole. With better understanding of the nature of the virus, infected mouse brain was used as the test antigen with normal brain tissue as the control. The difference between the control reactions and those produced by the antigen were such that Binkley and Love[23] facetiously remarked that it was necessary to employ a slide rule to calculate the results. On this basis the test results

were not convincing. With the still better understanding of the virus of lymphogranuloma venereum, growth in egg embryo culture has yielded a product which, in spite of its shortcomings, is regarded as a great advance over the original Frei product. The preparation of a more purified tuberculin is another recent example of improvement in technique.

16. *Lot of Antigen.* The variation in different lots of antigen prepared in the same manner is one of the unsolved problems in evaluation of cutaneous reactions to these antigens. Standardization of antigens has been sought by a number of investigators. Howell[133a], for example, tested guinea pigs experimentally infected with *Histoplasma capsulatum* and *Blastomyces dermatitidis*. He showed that the number of experimentally infected guinea pigs which reacted to histoplasmin, blastomycetin, or the heat-killed yeast-phase antigens depends upon the particular lot of antigen employed and upon its dilution; although antigens prepared from cultures of these organisms will give reactions in guinea pigs infected with either fungus, the percentage and size of these cross reactions are dependent upon the dosage of the particular antigen used. If the critical titers of these antigens are determined, and if these concentrations are used to study cross reactions, the degree of cross reaction between these antigens is small and the antigens are therefore relatively specific for guinea pigs experimentally infected with the homologous fungi. Howell further points out that the level or degree of sensitivity of the animals employed to determine the titer of an antigen must be considered. That is, if the sensitivity level is low, a high concentration of the antigen will have to be used to elicit a reaction, and therefore a false impression of the critical titer of the antigen will be obtained. Such high concentrations of the antigen will produce a high percentage of cross reactions. Smith[235] concurs in this view and in his experience there seems to be a large amount of a hypothetic common antigen in *B. dermatitidis* and *H. capsulatum* as subjects with clinical and subclinical histoplasma infections usually react both to histoplasmin and blastomycin. The size of the reaction to blastomycin is always smaller and disappears when more dilute antigens are used. He recommends as a practical procedure the subcutaneous use of histoplasmin, blastomycin and coccidioidin to determine which gives the greatest reaction.

Holm[131] has detailed a method of standardization of tuberculin employed in the State Serum Institute in Copenhagen. Smith and his associates[238] found great difficulties in setting up standards for coccidioidin. In 1941 Fernandez and Castro[89] standardized lepromin by a new method of preparation based on the different densities of *Mycobacterium leprae* and of tissues contained in ordinary lepromin.

Types of Reactions. In general it can be stated that one may anticipate 3 types of reactions after intradermal tests for the infections. The first, seen only rarely, is the immediate wheal reaction described by Kane as a union of the test substance "with its specific antibody at the site of inoculation." This combination may be irritating and lead to a histamine-like reaction. A wheal with a zone of erythema appears in about 15 minutes; it usually disappears in a few hours." The 2nd type of reaction is a delayed response, usually designated as the tuberculin or trichophytin type. This is the more usual type of reaction seen in chronic infections. Kane[146] rates this as a "true tissue allergy in which no circulating antibodies can be demonstrated."

The immediate and delayed types of reaction are essentially the same. The variation in response is due to differ-

ences in absorption of the antigen. Wells[266], and others showed that physical states determine the type of reaction produced. Addition of serum from normal and diseased patients (lymphogranuloma venereum—Howard and Strauss[132]) has no influence on the result of these tests.

The 3rd or eczematous or epidermal contact type of reaction to intradermal tests for infections is extremely rare.

The reactions in the Schick and Dick tests, although of the delaved type, deserve special mention as their occurrence depends on the inherent toxicity of the materials used for testing rather than tissue sensitivity. Their damaging effects are manifested in persons who have no specific neutralizing antitoxin. A positive Schick or Dick test, therefore, indicates susceptibility, and not, as in the tuberculin type of test, previous infection with the pathogenic agent, that may or may not have led to manifest resistance. Even in this type of test non-specific individual differences of the skin play a role which should not be neglected[258].

Dangers of Skin Tests. Intradermal tests are relatively free from certain untoward reactions which ordinarily need cause little concern. Among the undesirable effects described are: sensitization; various cutaneous reactions (hemorrhagic purpura; necrotic scarlatiniform eruptions[253]; local and focal flares of the presenting process; allergic shock; lymphadenopathy.) Merei[178] observed 3 cases in which diagnostic Mantoux tests were followed by symptoms and signs of a neuro-allergic lesion of the central nervous system (leukoencephalomyelitis).

Cross Reactions. Cross reactions to antigens from organisms causing chronic infections have been observed frequently and much effort has been expended in determining their extent and prevention. Emmons, Olson and Eldridge[79] investigated the clinical and experimental aspects of these reactions to antigens derived from fungi responsible for the deep mycoses. Robinson[215] also observed similar cross reactions to antigens prepared from Ducrey bacilli and from the virus of lymphogranuloma. The subject of specificity of the antigen for intradermal tests is so important and interpretation often so difficult that we give some data relating to the problem in several fungus diseases.

While many investigators had observed the unreliability of certain fungus antigens when used as diagnostic agents in skin testing, Emmons, Olson and Eldridge[79] maintained that one could not accept the specificity of a fungus antigen until it has been tested against other mycoses. Accordingly, they skin tested with histoplasmin guinea pigs and rabbits injected experimentally with other mycoses. They also studied patients with and without atypical pulmonary lesions, after initial testing with 0.1 cc. of a 1:1000 dilution of each antigen intradermally. Cross reactions between histoplasmin, blastomycin, coccidioidin and haplosporangin were demonstrated. Cross reactions between histoplasmin and blastomycin observed in animals were confirmed by the results of cutaneous tests in patients. Howell[133a] in 1947, however, continuing these experiments, arrived at other conclusions. Christie and Peterson[37a,b], working in Tennessee, encountered no false positive coccidioidin skin reactions in children and young adults. No coccidioidomycosis has been observed in this region. Of 125 persons tested, many reacted definitely to histoplasmin but none to coccidioidin. C. E. Smith and his co-workers[238] believed that coccidioidin is generally specific in patients with other systemic mycoses. Martin[171] observed no false positive cutaneous reactions to blastomycin, but did observe a false negative in a patient with

a generalized infection. Dublin and his co-workers[72] also reported a proven case of histoplasmosis in which the histoplasmin test was repeatedly negative. This usually occurs in terminal stages and is usually thought to be an exhaustion mechanism. Butt and Hoffman[31] found no cross reactions to blastomycin and sporotrichin in 8 patients with positive coccidioidin reactions. They found 18 additional individuals with negative reactions to all 3 antigens. Katzenstein[147] in skin tests on 36 patients with histoplasmin, coccidioidin, blastomycin and sporotrichin, found the antigens in the dilutions employed non-irritating and probably yielding no false positive reactions in persons not affected by a deep mycosis. In a later study of the occurrence of cross reactions in histoplasmin and coccidioidal infection, C. E. Smith and his colleagues[237] performed simultaneous coccidioidin and histoplasmin skin tests on normal military personnel and others undergoing coccidioidal infections. Among 3376 healthy persons with negative or equivocal reactions to coccidioidin, 26% reacted dominantly to histoplasmin. Equivocal and occasionally positive coccidioidin reactions in individuals who had no opportunity of acquiring coccidioidal infections were found exclusively in the group of histoplasmin reactors. The stronger the histoplasmin sensitivity, the more frequent and larger the non-specific reactions to coccidioidin. The non-specific coccidioidin reactions were not so great as to interfere with interpretation, especially when considered in the light of the reaction to appropriate dilution of histoplasmin. If strong (1:10) coccidioidin was used however, as it must be in some forms of coccidioidal infections, the hazard of a positive non-specific reaction was considerable.

They concluded that histoplasmin appears to have limitations due to its cross-reactions, but used in appropriate relative strength, it, and coccidioidin, are valuable in the diagnosis and epidemiological investigation of pulmonary lesions.

D. T. Smith[235] agrees that there is a small amount of an antigen common to *C. immitis, H. capsulatum* and *B. dermatitidis* and the reaction to blastomycin is always smaller and disappears when more dilute antigens are used. He advises for practical purposes that histoplasmin, blastomycin and coccidioidin be used simultaneously. Furcolow[105], in regard to specificity of the histoplasmin reaction, states that there is a specific histoplasmin skin reaction, but that cross reactions are very few and appear to be due to overdoses of skin-testing antigens. The skin tests in proved cases have been positive in most patients not critically ill. Those that were negative were tested near death. Tests should be repeated, as initial negatives may change to positive.

Thus it is obvious that the correct interpretation of a cutaneous reaction to an antigen depends on more than the cutaneous reaction: exposure data, the patients' clinical status and other factors are of great importance. In the following discussion of skin-tests for individual diseases, additional factors of specific interest to the particular disease will be mentioned.

FUNGUS DISEASES. Superficial Fungus Infections. Details on various cutaneous tests in diagnosis of fungus diseases have been discussed in detail in Lewis and Hopper's text[165], and Kligman and DeLamater's[154] recent compilation. We propose here to review some of these data in summary fashion, and others more extensively.

Fungus infections are usually divided into the superficial mycoses and the deep or systemic types. With regard to the trichophytin and the oidiomycin tests, it can be stated that in this country, since so many of the

population have had a fungus infection or harbor monilia, asymptomatically the value of these tests is relatively limited. In Europe where "athlete's foot" is relatively uncommon, Urbach and Gottlieb[254] believe the trichophytin test is of distinct value in the diagnosis of active ringworm. Lewis and Hopper[165] conclude from their experience that the value of fungus vaccines in diagnosis and treatment is not entirely clear. They believe that trichophytin is specific in the sense that it denotes sensitization by infection with a dermatophyte. Since not every person infected by fungi becomes sensitized, the test is not always diagnostic even though specific. As part of a complete study, they believe it has confirmatory value both in diagnosis and prognosis. The reactions to oidiomycin are so commonly attained that the results are useless for diagnosis, and Lewis and Hopper believe it should be abandoned. As an example of the type of results obtained from this test, Lewis, Hopper and Montgomery[166] found that 43% of the individuals with cutaneous moniliasis fail to react to oidiomycin and 46% of positive reactions were elicited in 192 individuals with no evidence of disease. Conant and his associates[42] agree that the test has no significant diagnostic value, in cutaneous moniliasis at least. Peck[200] rarely found positive reactions to oidiomycin in infants, but in older groups the percentage of positive reactions reaches almost 100%.

Two recent studies suggesting cross sensitivity between tuberculin and trichophytin are those of Falk[85] and Sulzberger and Baer[246].

Systemic Fungus Infections. *Actinomycosis.* Neuber[189a] as well as others[42] have reported that patients with actinomycosis, an infection caused by *Actinomyces bovis*, yield positive cutaneous reactions to intradermal injection of vaccines or of a filtrate of old broth-cultured actinomyces killed in an autoclave. Urbach and Gottlieb[254] think this reaction is specific and useful for diagnosis. Mathieson and his co-workers[173], however, observed 5 proven cases of actinomycosis with negative reactions to intracutaneous injections of a vaccine and positive reactions in persons free from actinomycosis. Kligman and DeLamater[154] believe the results with the vaccine are too contradictory to allow definitive estimate of the value of the skin test for this disease. On the whole, the experience reported in all the publications appears to be insufficient for any sort of significant analysis.

In the rare nocardiosis caused by *N. asteroides*, which Kligman and DeLamater[154] separate from actinomycosis, cutaneous sensitivity of the tuberculin type has been demonstrated in only 1 patient by Glover, Herrell, Heilman and Pfuetze[110].

Blastomycosis. First described by Gilchrist, North American blastomycosis has been a source of much interest, especially from the standpoint of skin sensitivity, other immune reactions and diagnosis. Those familiar with this disease realize the difficulties of establishing a definite diagnosis, as even persons of such great experience as Martin and Smith[172a] admit. Of 347 cases reported in the literature to 1937, they found only 184 which they accepted as undoubted blastomycosis. Primary infection in the lungs does not show characteristic roentgenographic findings and the process is often misdiagnosed tuberculosis until there is a dissemination of the infection with the appearance of subcutaneous abscesses or other lesions. We have had personal experience with a similar difficulty in a patient with bone lesions. While it is true that typical histologic features and especially mycologic study should be of much help in diagnosis, there appears to be considerable con-

fusion in the literature as to the various forms the organism assumes in tissue, and capable mycologists are still too few in number to be always available. Accordingly, it is obvious that there is definite need for a simple and specific test which would be negative in patients free of the disease and positive only in patients with the disease. A variety of epidermal tests for blastomycosis have been tried. (See Davis[60], Stober[242], Stein[239a], and Long[169]. Martin and Smith[172a], with a special antigen got positive reactions of the tuberculin type, though with occasional sterile abscesses. They encountered 4 positive reactions to the vaccines among 13 cases of systemic blastomycosis. Both of Peck, Martin and Hauser's[199] patients gave positive reactions to vaccine and the carbohydrate fraction of *B. dermatitidis*. Only one displayed a positive reaction to the protein fraction. To Nelson[188] in 1942 the results of testing for blastomycosis in human beings were inconclusive, whereas those in animals, as recorded by Davis[60] and by Long[169], yielded essentially negative results. In his own experiments, Nelson obtained positive results in guinea pigs experimentally infected with *B. dermatitidis*.

There are no definite data as to the time required for the development of a positive skin reaction to so-called blastomycin. On occasion, according to Martin and Smith[172b], the test may fail to become positive and, as noted above, the previously positive result may become negative in terminal stages[235]. Cross reactions, previously discussed, are greatest between histoplasmin and blastomycin. Fewer cross reactions are seen between either of these antigens with coccidioidin. *In spite of the shortcomings of blastomycin as a diagnostic test, Martin[171] felt that, while a negative reaction did not exclude blastomycosis, a positive reaction is diagnostic of the disease since he had not observed such reactions in patients with other diseases.*

Coccidioidomycosis (*C. immitis*). The cutaneous test in the diagnosis of coccidioidomycosis has been studied extensively, especially by C. E. Smith and his associates[238]. Their results form the basis for most of the material here presented. The coccidioidin now in use is a filtrate of liquid cultures of *C. immitis*, but there have been numerous precursors, summarized by C. E. Smith's group.

The usual reaction to coccidioidin is the tuberculin type. The immediate type of reaction was observed by Smith and his group[238] in persons who failed to develop a "delayed" type reaction and who were too recently in the endemic area to have acquired infections and lost sensitivity. They also elicited similar reactions with sterile distilled water and twice saw generalized urticaria. These reactions may have been coincidental. The delayed type of reaction appears in from 6 to 24 hours with a peak around 36 hours. The reaction is generally still present and sometimes maximal at 48 hours. Attempts at passive transfer of coccidioidin sensitivity by the Prausnitz-Küstner test usually failed. Since it is possible that testing with coccidioidin may be performed before sensitivity has developed, it is necessary to know the time of development of allergy after coccidioidal infection is acquired. The incubation period for coccidioidomycosis is from 10 days to 2 weeks (range from 7 to 28 days) and Smith, Beard, Whiting and Rosenberger[236] have demonstrated that about 60% of infections are completely masked. In 1940 Smith[234] found that coccidioidin sensitivity is established within 2 days to 3 weeks after onset. In the 1948 series Smith and his associates[238] found among 462 clinical cases of nonprogressive coccidioidal disease that 77 (one-eighth) gave negative re-

actions when tested with 1:100 coccidioidin during the 1st week of illness. Of 274 not previously positive, tested during the 2nd week of illness, 19 (6.7%) yielded negative results. Only 1% of 101 with an initial test later than the 2nd week was negative. The use of 1:100 dilution may account for the relatively earlier occurrence of positive results in this series. In patients with erythema nodosum the sensitivity is increased. There is some indication that during coccidioidal disease, if the person is highly sensitive, the skin test *per se* precipitated erythema nodosum. The duration of coccidioidin sensitivity is of great importance for interpretation. The fact that 80 to 90% of long-time residents in endemic areas react to coccidioidin indicates that the sensitivity persists. Although sensitivity to coccidioidin may wane, the loss is usually slow. Apparently re-exposure does not have any significant effect on maintaining sensitivity. A low level of coccidioidin sensitivity is usually associated with the dissemination of coccidioidal infection. The level of sensitivity has prognostic value but the establishment of coccidioidin sensitivity does not necessarily accompany clinical improvement. Just as loss of sensitivity to coccidioidin is ominous, so the development of sensitivity is encouraging, since increasing sensitivity has been noted when the infection improves.

Concerning cross reactions it is interesting that Tovar and Ramirez[251] who tested 1100 patients with intradermal coccidioidin, tuberculin and blastomycin tests, found no evidence of cross reaction with tuberculin or blastomycin.

Cohen and Burnip[39] studied coccidioidal infection in newborn infants in an endemic area and the earliest average age at which the first positive reaction to coccidioidin skin test may be obtained. The literature indicates a steady increase in positive reactors in children residing in an endemic area. For example, Gifford[107] in a study on pre-school and school children, found positive reactions in over half of the 2718 children tested. The percentage increased progressively from 17% among children who had lived in an endemic area less than 1 year to 77% among those who had lived there for 10 years or more. In 1949 Cohen[38] had observed an example of coccidioidal infection in an infant child of a mother who had had San Joaquin fever during pregnancy. To study the possibility of congenital infection Cohen and Burnip, therefore, did coccidioidin tests on 102 women immediately before or soon after delivery. Of these 102 women, 48 (47%) showed positive reactions. In addition, routine tests were made on 220 newborn. In Only 2 cases were there unequivocal positive reactions but Roentgen studies of the lungs in these 2 cases disclosed no abnormality. This indicates that coccidioidal infection is not transmitted congenitally. Skin testing of 595 infants and children disclosed that coccidioidal infection may be acquired as early as the age of 1 month.

Histoplasmosis. Histoplasmosis is a subacute to chronic infection caused by the fungus, *H. capsulatum*. It is characterized by a primary, usually benign and widely prevalent form and a secondary disseminated, relatively rare and often fatal form. Thus, the disease resembles coccidioidomycosis and tuberculosis. Before this new concept, which dates from 1948, the majority of cases, according to Furcolow[203], illustrated the disseminated, systemic form of the disease and supported the belief that the prognosis was almost hopeless, as most of the patients died. Reports of recovery from even disseminated infections have been increasing, and histoplasmosis is now thought to be a relatively benign di-

case. An interesting sidelight has been thrown by Cawley and Curtis[34] on the coexistence of this process with lymphoblastoma. Histoplasmosis as it occurs in animals has also received considerable study[77b,78,106]. Prior, Cole and Torbet[208] evaluated the histoplasmin reaction in spontaneous histoplasmosis in dogs; and Emmons[77b] has isolated *H. capsulatum* from samples of soil collected in Virginia. The literature on histoplasmosis in children was the special interest of Iams and his colleagues[136,137,264], and of Pryor[209]. The cutaneous and mucous membrane lesions of histoplasmosis were recently detailed by Miller, Keddie, Johnstone and Bostick[179], and by Curtis and Grekin[56].

Epidemiologic knowledge of histoplasmosis has been advanced by the histoplasmin test and the correlation of histoplasmin sensitivity with pulmonary calcification and tuberculin sensitivity[1,16,51,76,88,105,111,129,194,204,207,275,277]. In general pulmonary calcifications are statistically related to histoplasmin sensitivity, and are much more prevalent in communities where histoplasmin sensitivity is highly prevalent. Also, there is increasing reactivity with increasing years, the rate being influenced by localities. The acquisition of histoplasmin sensitivity is more rapid in early life than is tuberculin sensitivity and is in relationship to the development of pulmonary calcification. Peterson and Christie[204] concluded that in those children and young adults who have pulmonary calcifications but negative reactions to tuberculin, some cause other than tuberculosis must account for their calcified lesions. Kligman and De Lamater[154], however, point out that despite the massive data suggesting the existence of a benign form of pulmonary histoplasmosis as a cause of pulmonary calcification, final proof is lacking. The organism has only rarely been isolated from such pulmonary cases. Pulmonary calcification occurs also in individuals who are non-reactors to both histoplasmin and tuberculin.

Histoplasmin is a culture filtrate antigen similar to coccidioidin. Emmons, Olson and Eldridge[79] have described the method of preparation of histoplasmin. Salvin and Hottle[222] noted that although good yields of histoplasmin were obtained in media containing glucose, the substitution of starch, cellobrose, dextrin or glycogen produced far better yields. Cross and Howell[54] have isolated an immunologically active protein-free polysaccharide from histoplasmin. Scheff[227] found that animals gave positive reactions to a protein and polysaccharide fraction obtained from Histoplasma capsulatum. Salvin and Hottle[222] found that there is a close parallelism between the capacity of a given filtrate to elicit positive reactions and its ability to act as an antigen in complement fixation tests, so that the filtrates which fail to give cutaneous reactions fail to fix complement. Salvin and Hottle[222], therefore, suggest that the complement fixation test is a useful method of assaying the various lots of histoplasmin.

The positive histoplasmin reaction is of the tuberculin type (delayed). It is not inhibited by the anti-histaminic drugs[49] in contrast to tuberculin[223]. The histoplasmin sensitivity in cattle in Kansas, according to Furcolow and Ruhe[106], paralleled that in humans both as to age-specific rates and geographic distribution, thus suggesting that both cattle and man are infected from the same outside source. So few positive reactions are found in animals that they are apparently not an important reservoir of infection.

The effect of severe illness on histoplasmin reactions, cross reactions and other factors involved in the histoplasmin test have been discussed previously.

Sporotrichosis (caused by *Sp. schenckii*). As is the case in most of the deep mycotic infections, patients with sporotrichosis regularly yield positive reactions to intradermal injections of sporotrichosis antigen. In fact, there seems to have been little dispute in the literature regarding the specificity of this reaction and De Beurmann[62] believes that the presence of sporotrichosis may be ruled out as a diagnosis if the cutaneous test gives a negative reaction. The reaction to sporotrichosis antigen is usually of the delayed or tuberculin type; it may be severe and the test may provoke focal flares with malaise and lymphadenopathy[183]. The developments of cutaneous sensitivity have been observed as early as 5 days after experimental inoculation of a human volunteer[73].

Torulosis (caused by *T. histolytica*). According to Cox[50], torulosis is one of the few deep mycotic infections in which cutaneous sensitivity has not been demonstrated in animals or man. Although Kligman[153] worked out a method for the isolation of the polysaccharide capsular substance of Torula histolytica, this substance has not proved of value in skin testing of rabbits and mice.

Virus Diseases. *Herpes simplex.* Biberstein and Jessner[21,22] with an antigen (herpin) for cutaneous tests that they prepared for this virus disease got good, though not strictly specific results experimentally and also in 15 patients with regularly recurrent herpes simplex. Occasional and suspicious herpes, menstrual migraine and 29 "normal" cases gave negative results. Navarro Martin[186], however, claimed he got positive reactions to the antigen in all cases of herpes. Zuruckzoglu and Hruzek[276], who found positive reactions to sterilized blister fluid in everybody tested, concluded that everybody must have been infected with herpes at one time or another. Nagler[185a,b] in 1944 and 1946 confirmed the favorable results of Jessner and Biberstein; and Rose and co-workers[217] have also studied this antigen. However, there is little use for the herpes antigen in diagnosis because of the widespread presence of herpes antibody in so-called normal persons[130].

Lymphogranuloma venereum. We have already considered the development of a skin test antigen for the diagnosis of this now well known disease beginning with Frei's human pus antigen[17,158] in 1925 and culminating in the introduction of the yolk sac antigen (Lygranum) by Grace Rake and Shaffer[211] in 1940. Although the yolk sac material is more specific than the mouse brain preparation and as sensitive as the human pus material, there are still many gaps in the attainment of a satisfactory preparation for the specific diagnosis of this disease. Lygranum is, however, capable of preparation under standardized conditions, free from contamination and susceptible of having the virulence and dilution of the virus controlled. The technique for the test is essentially similar to that of the original Frei test. It is almost impossible to determine the time necessary for the reaction to cutaneous tests to become positive, but many believe that it only comes long after the infection is established. The best available clinical and experimental information suggested that the reactions became positive in 1 week to 6 months[126,190,263,271]. Once the positive reaction is established, it may persist for many years (30 years, Hellerström[126]; 21 years, Palmer *et al.* [195]). This tendency for the positive reaction to remain during the life of the patient (barring occasional cases reversed by therapy[12,225,239b]), definitely limits the usefulness of the test in determining the lymphogranuloma venereum character of a presenting lesion. Repeated testing has been known to induce posi-

tive reactions even in the absence of the disease[254]. The Frei test has been rated in large series as almost 100% specific by some authorities[43,49,59,90].

On the other hand, Brandt and Torpin[29]; Knott and his co-workers[155]; Robinson[215]; and Packer and Dulaney[193a] have questioned the reliability of the antigen. Cross reactions may occur in persons with other venereal diseases, especially chancroid and syphilis. Brandt and Torpin[29] interpret the high percentage of positive reactions in normal Negroes as falsely positive due to some peculiarity in the Negro skin. This idea is not acceptable to all investigators[99a,b,211]. False positive reactions have been observed in other diseases. False negative reactions are also a problem with the Frei test, and Frei[99a,b] himself suggested that under such circumstances an inverted or intravenous test be employed. In the inverted test, the sterilized pus from the patient is injected into the skin of a patient with proved lymphogranuloma venereum, producing a positive reaction.

Recently, attention has been called to the close relationship between the viruses of lymphogranuloma venereum, psittacosis, meningo-pneumonitis, trachoma, inclusion blenorrhea and the atypical pneumonia virus[74,75,151,205,211].

Mumps. In 1945 Enders, Cohen and Kane[80] reported that individuals with epidemic parotitis gave a tuberculin-like reaction following the intradermal injection of a heat inactivated suspension of parotid gland of a monkey infected with mumps virus. It was thought that a positive reaction indicated immunity while a negative response suggested that the individual was susceptible. In a systemic survey of almost 300 students in Harvard Medical School, a dermal reaction was obtained in 96% of those with a past history of mumps[81]. Of those who denied previous infection, half gave positive reactions; as 96% of these positive reactors had mumps complement-fixing antibodies, they were thought to be true positives. This supports the idea that frequently there are cases of asymptomatic or inapparent mumps. Habel[119] in 1943 adapted the virus of mumps to the chick embryo and has thus afforded a more available supply of the virus. Enders and his colleagues[80,81] found that the mumps virus skin reaction becomes positive several weeks after infection and that it might remain so for many years. Florman, Fischer and Moloshok[92], in a study of the results of skin testing, concluded that the so-called "Enders" test is of value in determining susceptibility to epidemic parotitis, and that view of the large number of clinically inapparent cases, it should prove useful in removing unnecessary concern about infection by parents who do not recall having had the disease.

Typhus Fever. Though much progress has been made in clarifying the clinical concept of this group of Rickettsial diseases, but little of value exists on cutaneous tests for the diagnosis of typhus. In 1931 Fleck and Hescheles[91] proposed a skin test for typhus employing an extract of Proteus X_{19} (Exanthin). As in the Schick and the Dick tests, a positive reaction was taken to indicate a healthy individual and a negative reaction either active disease or active disease in the preceding 4 years. In 1935 Goodman and Brodie[112] devised a new diagnostic test for typhus using formalized suspension of Rickettsiae. No confirmation of this work has appeared.

Virus Hepatitis. Henle, Drake, Henle and Stokes[127] have recently reported a skin test for infectious hepatitis (IH) which has been prepared from amniotic fluid of chick embryos injected with IH virus. Thus far, it has given apparently specifically positive skin re-

actions in all the individuals with past histories of spontaneous or induced IH tested. In contrast, the incidence of positive tests among cases of past serum hepatitis was no greater than that found among an adult group chosen at random.

Bacterial Diseases. *Tuberculosis.* The usefulness of the tuberculin test, probably the most widely used and studied cutaneous test for the diagnosis of infections is still a highly controversial subject. There are a number of excellent reviews on tuberculin to which the reader is referred: Kane[146], Sulzberger[245], Urbach and Gottlieb[254], Jacquelin and others[140], Thomas[248a], Seibert and others[228,229], Corper[47], Stilwell[241], and the extensive World Health Organization studies of Ustvedt[256].

During the past 10 years a marked change of attitude has appeared toward the value of the tuberculin test. In 1940 Sulzberger[245] after a critical review of the literature and his own experience, concluded that "*Tuberculin skin tests are of little or no diagnostic value in adults; their usefulness is limited to children who are sufficiently young to come within the class of those in whom previous tuberculous infection is exceptional.*" On the other hand, Stilwell[241] in 1948 concluded his comprehensive discussion of the changing concepts in tuberculin testing with the statement that "in the case of adults, the tuberculin test is becoming an important aid in general diagnosis, particularly when one is dealing with puzzling diseases of the thorax. The importance of this test will increase in future years as the incidence of tuberculosis continues to decrease. No longer valid is the assumption by the clinician that the results of tuberculin testing of adults are meaningless because of the preponderance of positive reactions among adults in previous decades." Kane[146], however, still questions whether a positive tuberculin test is an asset or a liability.

That greater confidence in the tuberculin test results is not entirely a matter of technical improvement is hardly questioned, in spite of the fact that Seibert's[228,229] purified protein derivative (PPD) is about 200 times as effective by weight as old tuberculin (OT), is much less variable in potency, and does not tend to produce false positive reactions upon repeated testing. Thomas[248a] found on the basis of 109 parallel tests in 79 patients with a wide variety of dermatoses that the purified protein derivative of tuberculin is equal to freshly prepared dilutions of a potent old tuberculin in detecting sensitized persons. She obtained no positive reactions with this substance in persons in whom they were not also elicited with old tuberculin, and no negative reactions occurred which were not confirmed by old tuberculin.

We shall not review the already well known technical details of tuberculin testing, and the interpretation of results. We have already referred to some of the factors which influence the outcome of the test (antihistaminics[102,116,223]; age[94,108]; the recent studies of the tuberculin patch test[184,198,259b]; or other modifications of the procedure[156,218]). The question of pulmonary calcification and skin tests has been discussed under histoplasmosis. Since most observers are agreed on the relative anergy to the tuberculin test in sarcoidosis[100,248b], further elaboration of this point is not necessary here. Our discussion, therefore, will be limited to the recent publications dealing with the significance of the tuberculin test in connection with BCG (Calmette-Guerin bacilli) inoculation[24,94,162,232,241], and the intradermal BCG test[61a,b,65,102,167,256,257]. (It might be mentioned in passing, that Frappier and Guy[98] recommended their BCG

scarification test as a practical means for detection of tuberculosis.)

The BCG test so-called is mentioned in connection with sarcoidosis[163,261a,b]. Ustvedt and Aaronsen[257] found this procedure preferable to tuberculin in diagnosis, especially in previously tuberculin-negative reactors who had received BCG vaccination. Although by their admission we are only at the beginning of our understanding of this field, the studies of Leider and Sulzberger[162] on the responses of the skin to BCG vaccinations in various categories of tuberculin sensitivity (see Sulzberger and Baer[246]) are timely.

According to Leider and Sulzberger, the usual responses of modern city dwellers to quantitative dilutions of old tuberculin Koch suggests that there are the following different degrees and kind of reaction or absence of reaction: 3 grades of sensitivity—normergy (degree of sensitivity usual in the age group of the particular community at time of testing), hyperergy (degree of sensitivity greater than the usual) and hypoergy (degree of sensitivity less than the usual)—and 3 types of absolute or relative insensitivity or anergy —native or original anergy (of the never infected); nonspecific, negative or absolute anergy (cachectic), and positive, specifically acquired relative anergy. Several of these types of response to tuberculin seem to differ from the others in basic cause, in principle and in effect.

They postulate a priori that the clinical courses of intracutaneous BCG vaccinations in subjects individually exhibiting the different types of tuberculin response must also differ. From the observations and reports of previous investigators it seems that the postulation of different responses to BCG vaccinations holds true for native and originally anergic persons and for tuberculin-sensitive persons (normergic and hyperergic). Their experiments confirmed this at least for the tuberculin-sensitive person and further demonstrated a different and characteristic 3rd type of response to BCG vaccination in persons with positive anergy.

From the observations and reports of others, it is fairly certain that response of persons with native or original anergy to BCG vaccination is in accord with the first part of Koch's fundamental experiment in the guinea pig (an incubation period of about 2 weeks during which tuberculin sensitivity is induced and consequent inception of a local lesion with a limited clinical course of 2 to 3 months).

The reaction of tuberculin-positive persons to BCG vaccination is shown by Leider and Sulzberger and in the reports of others to be like the second part of Koch's fundamental experiment; that is, rather than an incubation period, there is a reaction time of 24 to 48 hours after which the local lesion begins promptly and runs an accelerated course to healing in 2 to 3 weeks.

Response to BCG vaccination of the hypoergic, relatively or positively anergic person was found to be entirely different from the 2 distinct reactions just described by the results of BCG vaccinations of patients with sarcoidosis. Here intracutaneous inoculation with BCG vaccine results, after 5 to 7 days in a rather torpid, slowly growing papule which persists, seemingly indefinitely, as a papule or small plaque. Clinically the indurated papule or plaque mimics sarcoid lesions.

Leider and Sulzberger do not discuss implications as to the cause of sarcoidosis from the cutaneous and immunologic responses to BCG vaccination in patients with this disease, but they pose certain questions for further consideration.

Leprosy. In a general way there are 3 types of leprosy: 1, tuberculoid; 2, lepromatous, and 3, indeterminate. In the 1st type lesions contain none or

few leprosy bacilli, and in the 2nd there are myriads of organisms. The prognosis in the tuberculoid type is good and in the lepromatous poor. The lepromin test (Mitsuda test or lepromin test) utilizes sterilized and carbolized lepromatous tissues rich in bacilli. This is injected intradermally. It yields a negative reaction in lepromatous phase and a positive result in the tuberculoid type. In the indeterminate type it is positive or negative. The literature on the use of the lepromin test reveals much interesting data[8,221a,b]. In 1935 Bargehr[15] observed that cutaneous inoculations produced no reactions in persons who have never come in contact with leprosy patients. Positive reactions occur in individuals who have been in contact with lepers for some time, but who are themselves healthy (staff and personnel in leper colonies, relatives of lepers, persons in leprous countries); no reactions occurred in patients with demonstrable bacilli and symptoms of existing leprosy; positive reactions occur in persons who, either briefly or for some time, were afflicted with leprosy but in whom bacilli are no longer demonstrable; positive reactions occur in individuals who have received repeated inoculations of lepromin and, in rare cases, strongly positive reactions occur during the final phase of the disease (eruption or severe erythema).

Sarcoid, which clinically has been compared with leprosy, has yielded positive reactions to lepromin (3 of 10 cases gave positive reactions[265]; weak positive reactions in 5 cases[123]).

Miranda[181] obtained positive reactions to the lepromin test in 90% of 123 children vaccinated with BCG. Gines and Poletti[109] made similar observations.

From the standpoint of diagnosis, the lepromin test has failed to give positive reactions in patients with undoubted leprosy[35,45,64,118,196]. This has led to an almost uniform conclusion that the Mitsuda test is not useful in the diagnosis of leprosy, irrespective of its value in prognosis. An acceptable summary of the value of the lepromin test is that of Johansen, Erickson and Ross[144].

Brucellosis (*Undulant Fever*). The degree and regularity of occurrence of dermal sensitivity to Brucella antigens following brucellosis is such that its demonstration can be used as a diagnostic test[86,146,149,164,174]. Huddleson[134] found the cutaneous test of more value in diagnosis than the serum agglutination test. The 2 antigens used for skin testing are a heat-killed suspension of Brucella organisms and Brucellergen (so-called "nucleoprotein" from Brucella organisms[135]. While the 2 types of antigens appear to be similar in eliciting dermal sensitivity, the whole organism is more apt to cause local and systemic reactions. Brucellergen, in addition to its relatively greater safety, has lately been rated by Urschel[255] as the antigen of choice in routine skin testing. In testing for chronic brucellosis, the antigen is used in a dilution of 1:12,000.

A positive reaction to the skin tests is taken by certain workers as an indication of infection or past contact with one of the Brucella organisms. Gould and Huddleson[114] believe that if the test is negative, brucellosis can usually be ruled out. Diseased persons (up to 39%), however, whose infection is proved bacteriologically, have had negative reactions. As with many other skin tests for various diseases, therefore, a positive test may mean previous contact or past infection or an active disease while a negative test does not necessarily rule out previous infection.

Chancroid (caused by *H. ducreyi*). Often misdiagnosed for syphilis or vice versa, chancroid's chief importance now, since there is effective therapy for it, is the matter of dif-

ferentiation from other genitoinfectious diseases. Cutaneous tests for the detection of chancroid have been used for a long time abroad, but the Dmelcos vaccine was excluded from this country because of certain Public Health regulations. As an expedient Cole and Levin[41] in 1935 described the intradermal test employing either the sodermal test for chancroid with chancroid bubo pus, a procedure which was first suggested by Ito[138] and used by Reenstierna[212], Frei [99a,b], Bratzlavskij and Moreinis[30] among others. Greenblatt and Sanderson[117a,b], while confirming the high percentage of positive results in chancroid with the pus antigen, felt that the percentage of error militated against general acceptance. This is especially true, as there is available a more accurate diagnostic cutaneous test in the case of the bacillary antigen as prepared by Greenblatt and Sanderson[117a]. This contention was given firm status by Greenblatt and Sanderson's[117b] later trial of the bacillary antigen. They were able to announce that they, in collaboration with Lederle Laboratories, had achieved a standardized product. A comparative study of this preparation with the Greenblatt and Sanderson's previously used bacillary antigen, as well as the European Dmelcos preparation, indicates similarly uniform and specific reactions.

Saunders and his group[224] felt the American preparations were specific for diagnosis. They made 322 intradermal injections of Dmelcos vaccine, 210 of Greenblatt's vaccine and 151 of a commercial product in 107 cases of chancroid and 28 cases with a history of previous infection, 27 cases with buboes and positive Frei test, and 117 controls. Heyman, Beeson and Sheldon[128] stated that the cutaneous test for chancroid should never be relied on as the sole method of diagnosis although it may be of limited value as an adjuvant to other procedures. Greenblatt came to essentially the same conclusion. Dienst[66] believes that the Ducrey and Frei tests when used on the same patient may be valuable in differential diagnosis. Robinson[215], on the other hand, encountered cross reactions with the Frei and Ducrey tests.

Dienst[66] made the pertinent observation that the antigenicity of *H. ducreyi* as shown by the skin sensitivity in proven cases of chancroidal infection remains constant whether the test antigen is prepared from a virulent or an avirulent strain.

There is some divergent opinion in the literature as to when the skin test becomes positive after infection. The time given varies from 6 to 10 days to 5 weeks. Greenblatt and Sanderson[117b] obtained positive results by the 20th day while others have found the test uniformly positive by the time the buboes appear.

Gonorrhea. To date cutaneous tests for gonorrhea have not been of definitive value in the diagnosis of this disease, as healthy individuals yield positive reactions and persons undoubtedly infected show negative results[206,249]. Engel and Grundmann[82], however, found the compligon intradermoreaction for the diagnosis of gonorrhea gives information of an entirely general character of the immune status during the course of gonorrhea. The specificity of this reaction was confirmed by successful passive transfer of the hypersensitiveness by the Prausnitz Kuestner method. Casper[33], and Dmitriev[67], and Dmitriev and Demidowa[68] believe they have discovered a diagnostically useful antigen in gonopolysaccharide. Conrad and Wishengrad[44], and Corbus and Corbus[46] recommend bouillon filtrate as antigen for the test, and the latter authorities believe their modification may be used as a criterion for cure

since cured cases showed a negative result.

Pertussis. The whooping cough skin test is not intended for diagnostic purposes, but rather to determine susceptibility or immunity to the disease. In any event, the test is still in the experimental phase. In spite of much work (summarized by Kane[146]) with the intradermal test employing either the so-called "agglutinogen"[93] or a thermolabile toxin the results are unsatisfactory for diagnosis or the determination of susceptibility or immunity. This is also the conclusion of Miller, Ryan and Havard[180] who employed the agglutinogen skin test. Cravitz and Williams[52], however, considered the Strean[244a,b] test of definite value in determining susceptibility to pertussis when performed with a heated control.

Diphtheria and Scarlet Fever. The Schick and Dick tests, like other tests briefly mentioned, for certain diseases, cannot be considered as diagnostic procedures except in a limited sense, but rather as means for determining the general state of clinical susceptibility or resistance to diphtheria or scarlet fever respectively. In view of this fact, we are listing only a few of the numerous recent publications dealing with these tests: Kane[146], Worcester and Cheever[272], Cohen, Schneck and Dubow[40], Hahn[120], Rober[214], Jacobziner[139], Bernardin, Fvala and La Boccetta[19], and Bradley[28].

Miscellaneous Bacterial Infections. Skin tests of as yet limited and questionable value have been developed for glanders[254], rhinoscleroma[189b], tularemia [95a,b,c,d], and influenza[20]. Tularemia skin tests appear to have some value in diagnosis. In one test devised by Foshay, the injection of antitularense goat or horse serum is injected intradermally to detect circulating bacterial antigen such as might be present early in the disease. Friedewald and Hunt[103] felt that the results with this test were variable and unreliable so that its usefulness in diagnosis was limited.

Diseases of Uncertain Etiologic Type. *Sarcoidosis.* We follow here the definition of sarcoidosis adopted by the Conference on Sarcoid, (Natl. Res. Council, Feb. 11, 1948)[213]:

It should be noted that there is considerable controversy as to the cause of sarcoidosis in the literature, some maintaining that it is "anergic tuberculosis", syphilis, and others even show convincing evidence to suggest the similarity of this disease and leprosy. Recent demonstration that the "sarcoid reaction" may be produced by trauma, beryllium, talcum, silica, among others, indicates that we are nowhere near a clear concept of the etiology of sarcoidosis[159b]. Sulzberger and Baer[246] believe sarcoid is a peculiar immunologically determined form of reaction which can be caused by a number of different organisms, the tubercle bacillus being the frequent presumptive cause, at least in New York City and many parts of central Europe. While we tend to subscribe to this view, we feel that much evidence is still lacking to substantiate it.

Significant interest in the cutaneous test, specifically proposed for the diagnosis of sarcoidosis, originally by Williams and Nickerson in 1935[270] in this country, and by Kveim from Oslo in 1941[159a] (now generally called the Kveim test) is shown by the recent appearance of numerous contributions [7,57a,b,58,161,168,210a,b,c,187a,b,226]. The Kveim test consists in the intracutaneous injection of heated saline suspensions of tissue obtained from persons with active disease. Kveim found that after the transient inflammatory response caused by the trauma of such an injection had subsided, a small, indurated papule developed at the test site within a variable period of time. This delayed papular reaction was distinctive in that it often required weeks

to attain its maximum size. It usually remained visible for many months thereafter. Microscopic examination of tissue from sites of such reactions showed a histologic structure essentially the same as that of the lesions of sarcoidosis. Injections of Frei antigen and old tuberculin injected simultaneously with the Kveim material produced no comparable result and the sarcoid material yielded negative results when injected into normal persons or individuals with syphilis or lupus vulgaris. As a result of these observations Kveim concluded that his test was specific for sarcoidosis. He also believed, but without experimental proof, that the reaction was specific. Williams and Nickerson[270], using a test differing but little from Kveim's, found that their results, while not sufficient to offer conclusive evidence, suggest that the hypothesis that sarcoid is a virus disease may be correct and that an antigen may be prepared for diagnostic purposes. Appel[7] demonstrated the first example of a positive cutaneous reaction with an antigen prepared from the spleen of a sarcoid patient. Since Kveim's[159a,b] report other studies have confirmed and extended his original observations. These studies indicated that a positive Kveim reaction occurred frequently in patients with sarcoidosis even when there were no cutaneous lesions. On the other hand, there is considerable evidence that the Kveim reaction, rather than being a specific phenomenon, may be only a general cutaneous response on the part of persons with sarcoidosis to a variety of substances. Intracutaneous injection of saline suspensions of leukemic human lymph nodes (Putkonen 1945); killed tubercle bacilli[24,163,226,261a,b]; intracutaneous administration of suspensions of normal human spleen pulp (Nelson 1948). The histologic changes after some of these injections are those of the sarcoid reaction. The Kveim antigen has certain characteristics summarized by Leider[161] as follows:

Danbolt and Putkonen found that sarcoidal lymph tissue (except tonsil) yields the best antigen (the most sensitive and the most specific for sarcoid). Proper dilution, as determined by bioassay on previously tested good reactors, enhances specificity and results in fewer "false" positive reactions. The antigen is exceedingly thermostabile and keeps well under refrigeration. Lomholt found that antigen could be produced from tissues affected with leukoses. As mentioned before, Warfvinge produced reactions which he cautiously stated resemble the Kveim reaction with suspensions of both virulent, living and killed tubercle bacilli. His first subject suffered from both classic active tuberculosis and sarcoidosis simultaneously. The injection of living tubercle bacilli reproduced the histopathology of sarcoid and not the reinoculation effect of Koch's fundamental experiment. Putkonen confirmed both Lomholt and Warfvinge in showing that active antigen could be prepared from both leukemic tissue and from tubercle bacilli.

Leider[161] from his analysis of the literature thought the Kveim test to be of distinct diagnostic value in sarcoidosis, particularly in the internal forms where biopsy is difficult or impossible, or in the cutaneous forms where both clinical and histopathological changes are equivocal. Its specificity, according to Leider, is favorable in comparison with other tests. Nelson [187b], on the other hand, states that a characteristic Kveim reaction has been observed in certain types of cutaneous tuberculosis and even in normal persons with some antigens. He agrees with Leider that standardization of antigens is necessary. The slow reaction is an unfortunate desideratum. Leider believes that a more refined

antigen and accessible standardized antigen might make the test more useful and that if such an antigen might be found in tubercle bacilli themselves (such as B.C.G. vaccine, and perhaps in other micro-organisms) the test would contribute more clarification of the problem of the cause of sarcoidosis.

Nelson, in his study of the Kveim reaction in 24 cases of sarcoidosis, found that the reaction was positive in 11 of 15 patients with active disease. In none of the 9 cases of healed or inactive sarcoidosis in the group was a positive Kveim response obtained. All persons who showed a positive cutaneous reaction to the injection of Kveim antigen also showed a typical sarcoid-like response to the intracutaneous injection of suspensions of normal human spleen tissue. The capacity for these characteristic cutaneous reactions did not seem to have any consistent relation to the type of clinical involvement, to the degree of sensitivity to tuberculin or to changes in the values for certain blood constituents observed in sarcoidosis. While he believes the Kveim reaction is of little value in the diagnosis of sarcoidosis, Nelson thinks there is some evidence that it may be of occasional prognostic use in following the course of the disease.

Reiter's Disease. Reiter's disease has been described by Harkness[121a,b] in his informative reviews as being "characterized by a clinical syndrome consisting of a primary abacterial urethritis of venereal origin, bilateral conjunctivitis, polyarthritis, frequently balanitis, and sometimes keratodermia blenorrhagica, cardiac and other manifestations have been described. The etiology is unkown. There is an almost identical syndrome associated with the various types of dysentery (the primary focus of infection in these cases is the bowel and not the urethra) which is probably the same disease. There are also certain other diseases and reactions due to treatment which may simulate the syndrome very closely."

Although the causative organism of Reiter's disease has not been determined, and suggestions have varied from virus, pleuropneumonia organisms and even "burned-out" gonorrhea, attempts have been made to develop a cutaneous test for the diagnosis of this process. For example, Storm-Mathisen [243] reported on positive cutaneous tests with "active" and "inactive" tissue emulsions from the individual patient's lymph nodes and joint exudates. Positive reactions did not develop in various other diseases. Harkness[121a], employing a phenolized suspension of "L" organisms prepared by Henderson-Begg, made intradermal tests in normal subjects, in sensitized guinea-pigs, and control guinea-pigs and rabbits. However, an extensive trial, promising in the first place, was abandoned, owing to a fairly high percentage of false positive results.

Granuloma Inguinale (Venereum). Granuloma inguinale[197] is a disease of growing importance, and, while demonstration of Donovan bodies in smears, tissue or culture is of definitive diagnostic value, a specific cutaneous test is desirable for certain special cases. In spite of efforts in this direction, the results to date are not too encouraging. Kornblith[157] as well as Anderson, De Monbreun and Goodpasture[5] pioneered in this field.

Having successfully cultivated *D. granulomatis in vitro* in fresh egg yolk medium, Chen, Dienst and Greenblatt [36] conducted further studies to see whether antigen prepared from this source could be used for a skin test in granuloma inguinale and whether this culture was antigenically related to the disease. They give detailed directions for preparing an antigen and performing a skin test with *D. granulomatis* grown in fresh egg yolk medium. Since all granuloma patients, active

or "cured," had positive reaction, negative reaction may serve to rule out granuloma inguinale. Interpretation of positive reaction, on the other hand, should be guarded, as there are apparently other chronic infections that cause false positive reactions. Packer and Dulaney[193b], after trial of a skin test on 16 patients with verified granuloma inguinale employing 2 antigens, thought that this test has only limited usefulness and did not recommend it for routine use.

Protozoan Diseases. *Toxoplasmosis.* The clinical manifestations of toxoplasmosis caused by the protozoan, *T. gondii*, have been detailed by Frenkel[101a,b]. Among the diagnostic procedures for this infection is a cutaneous test which Frenkel maintains is a most useful simple aid in the diagnosis of past or latent toxoplasmosis, whenever isolation of the causative organism is not feasible. Intradermal injections of suitable dilutions of toxoplasmin (derived from sediment of mouse peritoneal fluids rich in toxoplasma, inactivated cell bodies broken up, standardized, tested for sterility and diluted in phenolized saline solution) calls forth a tuberculin type of reaction in certain patients. The cutaneous test is most useful in the diagnosis of chronic toxoplasmosis. Patients with the acute disease do not acquire cutaneous sensitivity early enough for the test to be of value in diagnosis. Almost simultaneously, Warren and Russ[262] reported that an extract of toxoplasma infected chorioallantoic membranes contains a substance which also elicited a delayed cutaneous inflammatory reaction in an individual possessing antibodies for toxoplasma. Following this report Sabin (see Feldman and Sabin[87]) observed that in people whose serum contained toxoplasmic antibodies there appears 30 to 48 hours after intracutaneous injection, a distinct, severe inflammatory reaction at the sites inoculated with the extract of toxoplasma injected chorioallantoic membranes but not at the sites inoculated with the normal membranes. No such reaction was found in individuals whose serum was free of toxoplasma antibodies. Sabin, Feldman and Warren[220] in a comparative study of recently developed serologic methods and the skin test found that while the cutaneous test had little or no diagnostic value, it might, nevertheless, be useful for population surveys as an index to the probable incidence of inapparent toxoplasmosis. Feldman and Sabin[87] in one such study of 142 people aged 3 months to 81 years who at the time happened to be in the Cincinnati area listed the incidence of positive reactions among at least 20 individuals in each age group. Since no agent having an antigen in common with Toxoplasma and capable of giving rise to antibodies for this protozoan parasite has been found thus far, one must consider the possibility that inapparent infection with Toxoplasma may be widespread, although it is rather curious that the incidence of antibodies (and presumably infection) should rise so sharply after the 20th year of life. The toxoplasmic skin test is not useful for diagnosis because a strongly positive test bears no relationship to titer of antibody and a negative test is encountered too often in the presence of antibody.

Trichomonas Infection. Adler and Sadowsky[2] prepared bacteria-free cultures of *T. vaginalis* and made a fairly satisfactory antigen for skin testing of patients with and without this vaginal infection. Because microscopic examination for the protozoa gives better results, the authors do not recommend their skin test.

Leishmaniasis (Oriental Sore). The intradermal test for leishmaniasis has been studied extensively by Wagener[260], Jessner and Amster[142], Montenegro[182], Dubovskoy[71], Berberian[18],

Dostrovsky[69a,b], Dostrovsky and Sagher[70], and by Sagher[221a,b,c]. The characteristics of the reaction have been defined by Dostrovsky[69a,b].

The test is of reasonable specificity and a sample of recent discussion of its value in diagnosis is given by Sagher who not only has worked extensively with the test, but has collated the literature as well.

In Oriental sore Dostrovsky and Sagher[70] report their experience with various diagnostic methods in 434 cases of Oriental sore, with special reference to the intracutaneous test with L. vaccine. The specificity of the test was 91.6%. Nonspecific results were observed in 6.3% of a control series of 144 cases. They were also able to demonstrate a positive transfer test (Prausnitz-Kuestner) in 4 patients. Sagher showed that the quantitatively evaluated intracutaneous test yielded hyperergic reactions in recurrent leishmaniasis, but was anergic or hypoergic when done in the scars of lesions of leishmaniasis. On the other hand, the test showed the same reaction as in normal skin when performed in scars of vaccination or trauma in the same patients. De Blasi developed a new antigen which proved to be highly specific.

In an attempt to clarify the mechanism of the Leishmania test, Dostrovsky inoculated 6 human volunteers who never had a leishmania infection. Typical leishmania lesions developed rapidly; the short incubation period was most probably due to the massive doses used in the experimental infections (at least 2 million flagellatae as against 2000 flagellatae estimated as being introduced in "spontaneous" infections). The leishmania test became first positive 72 hours after the inoculation and, thereafter, became gradually more marked. It could be elicited during a follow-up period of 3 years even after complete healing of the lesions of inoculation and did not differ in intensity nor in time of appearance whether the test was done close to or more distant from the site of the inoculation.

Spirochetal Disease. *Syphilis.* Urbach and Beerman[252] have recently reviewed the status of the Luetin test. They observe that tests with organ luetin (prepared by extracting mature syphilomas from the testicles of rabbits) are, under certain conditions, strictly specific. Thus, while there is no response in the primary and secondary stages, positive reactions occur in most cases of acquired syphilis in the tertiary stage and in congenital syphilis, parenchymatous keratitis, and "malignant syphilis."

The reaction appears as a sharply demarcated, elevated, erythema, reaching a maximum after 48 hours. Nonspecific reactions are usually macular, not clearly defined, and disappear within 48 hours. A positive culture luetin reaction presents a papular lesion, in contrast to the sharply demarcated, reddened urticarial plaque. They emphasize that most of the adverse reports on the nonspecificity of luetin refer to work with culture luetin.

Certain conditions must be observed. Nonspecific reactions to luetin can be evoked in normal individuals, by previous administration of halogen. The patient must avoid any great quantities of halogens before the skin test and control tests must be performed. By carefully performing the necessary control, Urbach was able to employ organ luetin for diagnostic purposes. Moreover, by administering intravenous luetin therapy in cases of treatment-resistant malignant syphilis, Planner produced changes which seemed to increase the efficacy of arsphenamines.

More recently Rottmann[219a,b] made efforts to revive the luetin test. He be-

lieves that repeating the test in 1 week after the initial one gives reliable information.

Helminthic Disease. *Trichinosis.* Bachman[13] in 1928 introduced skin tests for trichinosis. These tests made with trichinella extracts are useful aids in the diagnosis of this disease. Bachman used a 1:10,000 dilution of a saline extract of powdered larvae of *T. spiralis* free from the tissue of the host in which the parasites developed. McNaught[177] pointed out that the positive reaction occurs early in the course of the infection (from the 3rd to the 10th day of illness) or it may persist for a long time (Gould[113]) in chronic cases. Augustine and Theiler[10] found the test more accurate in hogs than was microscopic search for the organism in muscle. McCoy and his colleagues[175] found the test positive in 92% of patients tested 2 to 6 weeks after the onset of the infection. Urbach and Gottlieb[254], however, felt that unless the clinical symptoms of trichinosis are present, the cutaneous test does not have diagnostic value. If the test is negative in the first days of the infection, but becomes positive after the 3rd week, it is of diagnostic significance. If the test is negative repeatedly in the presence of a negative precipitation test in the serum after a month's illness it excludes the presence of the disease. Fulminating disease, however, may be accompanied by a negative test. Cross reactions may occur with cysticercosis. More recent reports have contributed little new beyond the confirmation of the reliability of the test and the factors which may influence the outcome of the procedure.

Aikawa, Harrell and Helsabeck[3] found that acid pepsin and alkaline trypsin digestion of *T. spiralis* antigen did not destroy its antigenicity for dogs, as measured by skin tests and flocculation tests on serum. The more marked reactivity of the skin test as compared with the flocculation test suggests that the same antigen may not be responsible for both reactions. Failure of proteolytic digestion to destroy the antigens suggests that the antigenic fraction of *T. spiralis* is not solely a protein.

Harrell and Halsabeck[122] found no biologic cross reaction was detected by skin tests in rabbits infected simultaneously with bovine *M. tuberculosis* and *T. spiralis*. Simultaneous infection with bovine tuberculosis did not increase the intensity of trichinosis infections in rabbits.

Harrell and his co-workers[124] observed no correlation between the trichinella skin test and the tuberculin reaction.

Filariasis. A variety of antigens has been employed for skin testing in patients suspected of having filariasis; filaria from dog's heart gives 90% positive reactions in patients infected with *F. (Wuchereria) bancrofti*[83,247]; *D. immitis* extract on the basis of group specific rather than species specific [27,250]; Litomosoides antigen made from this filarial worm found in the pleural cavity of the cotton rat[55] filarid embryoas from *D. immitis* from infected dogs[97].

There is considerable disagreement as to the value of the intradermal test for filariasis. Although King[152], after using the procedure in a large number of carefully observed cases, concluded that it constitutes a valuable adjunct in diagnosis (90% effective), Oliver-Gonzalez and Morales[191] found the test fairly nonspecific in a group of 180 Puerto Ricans. They thought the nonspecificity may be attributed to cross reactions with other nematodes as a high incidence of infection with intestinal parasites was encountered in this group of microfilaria positive and negative individuals. Wharton and Stelma[269] thought the test from the diagnostic point of view had 2 weak-

nesses; 1, that it is unable to differentiate infections of different species of filariae, and 2, as generally employed, about 10% of the tests give false positive reactions with control individuals. The first of these is inherent in the nature of the antigen which is group specific rather than species specific. Bozicewich and Hutter[27] attempted to overcome the 2nd difficulty by greatly diluting the antigen and reducing the dose and claimed to have greatly enhanced the specificity of the test.

In a study involving 215 persons at the public hospital and almshouse at Georgetown, British Guinana, Wharton[267a,b] found that the antigen was even more effective than previously estimated and he recommended it again for its dependability, safety, ease of application and time-saving character. Wharton, Cuervo and Moyer[268] found in addition that in skin tests for filariasis, cross retractions with intestinal parasites such as Ascaris do not ordinarily occur.

Zeligs[274] used on 200 subjects an antigen consisting of a saline extract of dried *D. immitis* standardized to contain 500 protein units (0.0005 mg. protein) per cc. of solution. Of the 126 patients with filariasis, only 75 had positive reactions. Of 21 patients who were exposed to filariasis in the Samoa area without symptoms of the disease, 29% had positive reactions. Of 53 patients who had probably not been exposed to filariasis, 19% yielded positive results. In addition, 5 patients with *Schistosomiasis japonica* produced 3 positive results. Franks, Chenowith and Stoll[96] tested over 400 patients with an antigen prepared from the microfilariae of *D. immitis*. The optimal dilution was found to be 1:1000 as compared to 1:8000 for adult worm antigen. The reactivity of the test antigen in a filarial patient appears to be influenced by the clinical stage of the disease. The authors believe the microfilarial antigen has definite advantages over that made from adult worms.

Schistosomiasis japonica. Various antigens have been employed in the immunologic diagnosis of schistosomiasis. The earlier work in this field has been collected by Wright, Bozicevich, Brady and Bauman[273]. In the earlier literature, the comprehensive report of Kan[145] is worth citing. Oliver-Gonzalez and Pratt[192] reported 96 individuals passing ova of *S. mansonii* reacted positively to antigen prepared either from cercariae or adult *S. mansonii*. These authors believed that infections with nematodes provoke *no* cross reactions with antigens in question since 19 persons harboring *Ascaris lumbricoides, Necator americanus, Trichuris trichiura*, and 10 individuals with *Wuchereria bancrofti*, gave uniformly negative tests.

Wright and his co-workers were interested in recognition during the *acute* stages. In summary, they found that *intradermal tests* with antigen prepared from adult *S. mansonii* (dilution 1:1000 on a dry weight basis) failed to elicit positive reactions in military personnel exposed to *S. japonica* 4 to 5 months previously. However, the same material evoked positive reactions in 22 of 28 chronic cases among civilians. A total of 87 (83.7%) of 104 individuals infected with *S. japonicum*, as indicated by stool findings, was positive on the *flocculation test*, while *all* of 29 chronic cases among civilians reacted positively.

Alves and Blair[4] thought that routine microscopy in the diagnosis of schistosomiasis is inaccurate and expensive. A higher proportion of cases of schistosomiasis is revealed by use of a cercarial antigen for skin testing than can be detected even by repeated microscopic examination. They did not encounter a negative skin test in patients passing eggs. The test could be used as rapid and accurate "screen" test. The

skin test becomes negative when patient is cured. It thus may be used as indicating the need for further treatment.

Augustine and Lherisson[9] recently pointed out that certain of the false positive skin reactions obtained with *D. immitis* antigen in suspected cases of human filariasis may be attributable to immune responses produced in man by repeated exposures to the infective filarial larvae of the lower vertebrates. Since some schistosomes have been shown to have a common antigenic complex[84,148,150,273], Cort[48] questioned whether in a comparable manner to that shown for filaria by Augustine and Lherisson[9] repeated exposures to the dermatitis producing schistosome cercariae might produce a response which would account for the false positive immunological reactions encountered in studies on human schistosomiasis. In attempting to solve this problem experimentally, Augustine and Weller[11] developed an effective method for the concentration of living dermatitis producing schistosome cercariae by utilizing the positive phototropic and negative geotropic reactions of the cercariae.

Echinococcosis. The Casoni test is widely used for the diagnosis of echinococcus disease. In spite of the fact that the test is group specific and human hydatid cyst fluid is difficult to obtain rabbit cysticercus[216] and sheep or cow echinococcal fluid[63] may be used as the antigen. There is an immediate urticarial reaction described by Casoni[32] and a delayed papular type of response. An anonymous review[6] on this test has recently appeared.

Summary. These data on cutaneous tests in certain infections on the whole indicate that there is still much unknown about this problem. Recognition of the numerous factors involved in interpretation of these tests may in time militate against their widespread application in clinical practice.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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ANTIHISTAMINIC DRUGS AND THE COMMON COLD: A CRITICAL REVIEW

By NOAH D. FABRICANT, M.D.

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DESPITE a burst of advertising pyrotechnics seldom seen in the field of medicine, the American medical profession is beginning to learn that the common cold cannot be liquidated by extravagent and irresponsible claims in behalf of antihistaminic drugs. The facts of the matter are that no substance or combination of substances currently available can be relied on to prevent or cure the common cold. Controlled studies of products which now appear on the market reveal that the sensational advertising claims are not justified by valid evidence. The American public has been asked repeatedly to spend huge sums of money unnecessarily on these "miracle drugs". It will continue to do so until it is educated by physicians to the foolishness of such practice.

The notion that allergy is mainly responsible for the common cold has never been substantiated by reliable investigators, although Fox and Livingston[11] consider the common cold to be an allergic response to contact with a specific protein, namely the cold virus and its products, and Brewster[3] maintains that the common cold begins as an allergic reaction. While antihistaminic drugs are neither antiviricidal, antibactericidal nor antibacteriostatic, antihistamine therapy of the common cold has been based upon the unproved assumption that an allergic component is involved in the etiology of the infectious common cold.

That antihistaminic drugs are not innocuous is becoming progressively evident. In an inquiry to 247 physicians, 223 reported to Arbesman[1] the development of such side-effects as drowsiness and dizziness among patients taking antihistaminic drugs for the common cold. Virtually all antihistaminic drugs possess sedative properties in moderate dosages and are cerebral excitants in large dosages. Other side-effects which may occur are frequent urination, dryness of the mouth, insomnia, cardiac excitation, gastrointestinal disturbances, headache, fever, blurred vision, tinnitus, skin rash, and nervousness. Instances have been reported of users of antihistaminic drugs falling asleep at work, while operating machinery or driving automobiles. Children have died following the accidental ingestion of large dosages of antihistaminic drugs. These agents may have profound effects not only on the central nervous system and the genitourinary system but on the hematopoietic system as well. Crumbley[6] calls attention to the occurrence of hemolytic anemia in 3 patients who had received antihistaminic drugs over long periods of time; Drake[8] describes a case of agranulocytosis following the administration of methaphenilene hydrochloride (diatrin); and Cahan[4], and

Hilker[13] report agranulocytosis due to tripelennamine (pyribenzamine). As a result of the over-the-counter sale of antihistaminic drugs, careless and habitual use may be expected and the medical profession should anticipate similar serious reactions.

Treatment of the common cold is influenced by so many factors that only a rigidly controlled study eliminating as many variables as possible can be relied upon for valid conclusions. Wary investigators always concern themselves with such factors as the unreliability of subjective impressions; the suggestibility of patients as well as physicians; the fluctuations of a patient's degree of immunity; the difficulty of objective diagnosis of the common cold; confusion with vasomotor rhinitis and nasal allergy; and the matter of transient vasomotor instability. A great many episodes involving sneezing and early nasal discomfiture never materialize into true infectious colds; basically they involve transitory vasomotor mucosal changes in the nasal cavity as the result of chilling, drafts, fatigue, emotional disturbances and menses. The spontaneous variation in the duration of the common cold has been demonstrated by Diehl[7] who found that 35% of patients report good results. It is because so many patients believe in the efficacy of therapy that it is possible to convince the general public that almost any new treatment for the common cold is of value. Diehl found that some of the reports from people receiving a placebo containing lactose would have served as admirable testimonials for this inert material.

In 1947 Brewster[3] wrote the first of a series of papers zealously advocating the use of antihistaminic drugs in the treatment of the common cold. His reports included the use of diphenhydramine (benadryl) hydrochloride; tripelennamine (pyribenzamine) hydrochloride; pyranisamine maleate (neoantergan); and methapyrilene (histadyl and thenylene) hydrochloride. In his 1949 series, all symptoms were aborted in 19 of 21 patients who began medication within 1 hour, and in 48 of 55 patients who commenced medication within 2 hours after the onset. Brewster accepted the patient's diagnosis of a cold when the examiner failed to discover evidence to disprove it. None of his studies established the diagnosis of a common cold beyond reasonable doubt, and patients with allergy were not adequately excluded. The high percentage of cures (32%) with placebo medication demonstrated the validity of Diehl's observation.

Gordon[12] described the use of diphenhydramine, tripelennamine and phenindamine tartrate (thephorin) in the treatment of infections of the upper respiratory tract. His study lacked controls and his methods of evaluation and interpretation of results were inadequate. In another uncontrolled study, Murray[15] asserted that tripelennamine produced more so-called cures and more relief than any other treatment in a group of subjects with head colds. His patients "were all very sure they had a cold or that a head cold was starting." The most enthusiastic results were described by Arminio and Sweet[2] who employed thonzylamine (neohetramine) hydrochloride in the prophylaxis and treatment of the common cold among subjects restricted in their activity. Phillips and Fishbein[16] used caubren compound, a mixture of chlorothen citrate, acetophenetidin and caffeine, for the treatment of colds in an industrial plant and found the average duration of colds to be shorter for the group given caubren than for the group given acetylsalicylic acid.

The failure of the antihistaminic drugs in the common cold has been demonstrated in a series of carefully controlled studies conducted by various investigators at Cornell University, the

Western Reserve University School of Medicine, the University of Minnesota, the University of Illinois College of Medicine, the Chicago College of Optometry, the United States Naval Training Station at Great Lakes, Illinois, and at West Point.

In the study conducted at the Cornell University Student Medical Clinic by Shaw and Wightman[18], a total of 443 students were divided, following examination to make certain the presence of actual cold symptoms, into 2 groups. One group, numbering 228 subjects, received a 3-day supply of Antistine (2 - phenyl-benzylaminomethylimidazoline hydrochloride) in 50 mg. dosage, while 215 members of a second group received a placebo of identical appearance. On each of 3 subsequent days, the patients were questioned regarding each of their symptoms. Of those who received the placebo, 107 (50%) believed that the tablets had been of benefit, while of those who received the antihistaminic drug, 122 (53%) thought it had helped them. In an analysis of the individual symptoms, sore throat, running or congested nose, and malaise were aided equally by the placebo and the antihistaminic drug. These investigators question the beneficial effect of the antihistaminic drug in the treatment of the common cold.

Two major studies were undertaken by Feller[10] and his associates at Western Reserve University School of Medicine to test the value of antihistaminic drugs in the treatment and prevention of the common cold and undifferentiated respiratory diseases. The first was conducted on a group of 55 families in whom the occurrence of illnesses had been continuously observed in minute detail over a 2 year period as part of another study. During December, 1949, and January, 1950, 376 respiratory illnesses occurred in 203 of the 253 persons comprising the 55 families. Eighty-seven illnesses were treated with antihistaminic drugs, and 289 were not so treated. Clinical classification showed that three-fourths of both the treated and control illnesses were compatible with a diagnosis of the common cold, with the remaining undifferentiated respiratory illnesses likewise proportionately divided. In almost all instances the drugs employed were purchased over the counter and were used in dosages of 25 mg. or equivalent amounts. A total of 7 antihistaminic compounds were utilized and included Thonzylamine hydrochloride (Anahist; Neohetramine; Resistabs), Chlorprophenpyridamine maleate (Chlor-Trimeton; Coricidin), Tripelennamine hydrochloride (Pyribenzamine), Diphenhydramine hydrochloride (Benadryl), Prophenpyridamine (Inhiston), Chlorcyclizine hydrochloride (Perazil), and Pyrinisamine maleate (Neo-Hist). Comparison of the duration of all treated and control illnesses revealed that the antihistaminic drugs had no beneficial effect, regardless of dosage. Similarly, no benefit took place either in the common cold or in the other undifferentiated respiratory illnesses. The duration of nasal symptoms was not abbreviated by administration of the antihistaminic drugs. No beneficial effect could be demonstrated when "adequate" dosage was defined as 8 or more instead of 3 or more doses. Furthermore, it was impossible to detect a significant difference between the durations of the treated and untreated illnesses. From the data it was concluded that the antihistaminic drugs were ineffective in this group as therapeutic agents for the common cold and other undifferentiated respiratory diseases.

The second study at Western Reserve University School of Medicine was designed to evaluate the prophylactic and therapeutic effect of 2 antihistaminic drugs, Pyrrolazote and Neohetramine, on the occurrence and subsequent course of common colds de-

veloping after the experimental inoculation of normal volunteers. In one experiment, 18 volunteers were inoculated with cold virus administered intranasally and given Pyrathiazine hydrochloride (Pyrrolazote) 4 times daily in dosages of 50 mg. An inert placebo served as a control. Administration was begun 2 hours before inoculation and was continued for 5 days. In the 2nd experiment 31 volunteers participated. Ten subjects were inoculated with infectious nasal washings and given 4 Neohetramine tablets daily for 5 days, with 3 taken before inoculation. Another similar group was inoculated with infectious nasal washings and given placebos; in addition, 11 subjects were inoculated with sterile milk.

The administration of these antihistaminic drugs failed to prevent the development of the common cold despite the fact that medication was begun before inoculation and was continued for several days thereafter. In the 1st experiment there were equal numbers of well established colds in the groups that received the antihistaminic drug and the placebo. In the 2nd experiment there were 6 colds in the treated group, whereas there were but 3 in the placebo group. Of the 11 subjects who were inoculated with sterile milk, 3 developed colds; two of these were taking the antihistaminic drugs. The antihistaminic drugs had no favorable effect on the severity of the illnesses, the duration of the symptoms, or the length of the incubation periods. No appreciable differences in the duration of nasal symptoms, throat symptoms or cough were detected in the 14 colds treated with antihistaminic drugs as compared to the 10 colds treated with placebos.

At the University of Minnesota, Cowan and Diehl[5] conducted a controlled study among students especially subject to the common cold for the purpose of evaluating the antihistaminic drugs as a method of treatment. The students were supposedly non-allergic. Five preparations were tested: Pyribenzamine (tripelennamine hydrochloride): Thephorin (phenindamine tartrate); Theophorin plus ascorbic acid; ascorbic acid; and a placebo. Students were given a box of medicine with written instructions to take 1 dose every 4 hours until the cold was definitely "cured" or until the medicine (10 doses) was used up. Three hundred and sixty-seven students were treated for 980 colds during the period between December, 1948, and April, 1949. In this study there was no indication that ascorbic acid alone, Thephorin alone, Thephorin plus ascorbic acid, or Pyribenzamine have any important effect on the duration or severity of the common cold.

The study at West Point conducted by Hoagland[14] and his associates was confined to 190 young men in military service who developed head colds. Five preparations were employed: Pyribenzamine (tripelennamine hydrochloride); Tagathan (chlorothen citrate); placebo; Pyribenzamine nasal spray; and a placebo nasal spray. The oral antihistaminic drugs were given in dosages of 50 mg. 5 times daily for 3 days. The nasal sprays were used for 3 days on a schedule of every 3 to 4 hours. The investigation disclosed that "cures" within 24 hours were reported by 16% of the patients given antihistaminic drugs orally, while 27% of the patients receiving oral and intranasal placebos reported cure within 24 hours. There was no significant difference in the proportion of cures reported by patients receiving oral antihistaminic drugs and those receiving oral placebos. Essentially the same proportion of patients received no benefit from either type of treatment. The effect of Pyribenzamine administered in the form of nasal sprays was essentially the same as the

effect of inert materials given orally and intranasally.

Seal[17] carried out an extensive investigation at the United States Naval Training Station at Great Lakes, Illinois, with 1964 of the station personnel as subjects. The Navy study was divided into 4 phases and includes prophylactic and therapeutic trials of 4 antihistaminic drugs — thonzylamine, chlorophenypyridamine, doxylamine, and pyrathiazine. In the 1st phase of the investigation, 1103 subjects were divided into 3 groups. The first group of 352 patients received daily doses of 100 mg. of one of the antihistaminic drugs; placebos were given daily to 337 members of the second group; while a 3rd group of 414 received no medication whatsoever. During the period of the test, 161 (46%) of those in the 1st group developed colds, 166 (49%) of the 2nd group developed colds, while 195 (47%) of the third group contracted colds. This phase of the investigation was conducted at a time when the incidence of colds and other infections of the upper respiratory tract was high and all subjects were under constant medical observation. Seal concluded that antihistaminic drugs did not effectively decrease the number of men requiring attention at the dispensary, the number of admissions, or in any way alter the symptomatology among the patients.

In the 2nd phase of the Great Lakes study, investigation was made of the prophylactic value of the antihistaminic drugs among subjects who had been examined to eliminate those already having colds. One hundred and eighteen subjects received 75 mg. of an antihistaminic drug 3 times daily, 116 subjects were given 30 mg. 3 times daily, while 123 received placebos on a similar time schedule. In the 3rd phase of the study, 159 members of the Waves, divided into 3 groups, were treated with an antihistaminic drug, a preparation containing atropine, and a placebo. In the antihistamine group, 2% of the patients recovered within 24 hours, 18% within 48 hours, and 52% within 5 days. In the atropine group, 2% of the patients were relieved of their symptoms within 24 hours, 6% within 48 hours, and 58% within 5 days. In the placebo group, 4% of the patients recovered within 24 hours, 19% within 48 hours, and 47% within 5 days. In the 4th phase of the investigation, 370 subjects participated, half being given antihistaminic drugs, half placebos. These patients included the wives and children (over 12 years of age) of naval personnel; 38% of those individuals taking antihistaminic drugs and 38% of those taking placebos had colds during the same period. From these various group studies, Seal concluded that no evidence could be found to demonstrate that antihistaminic drugs are effective in the common cold.

Fabricant[9] carried out a carefully controlled study among the students of the University of Illinois College of Medicine and the Chicago College of Optometry to determine the effect of various antihistaminic drugs on the course of the common cold during January, 1950, to April, 1950. The antihistaminic drugs under observation included Neohetramine, Pyribenzamine, Diatrin, Chlor-Trimeton, Benadryl and Decapryn. The selection of drugs and placebos for clinical trial was determined by means of random selection. It was concluded from this investigation that there is no valid evidence that the antihistaminic drugs now available have any effect on the common cold. The study demonstrates that antihistaminic drugs do not prevent, abort, shorten, curtail, reduce or stop the common cold. It was observed that antihistaminic drugs are no more effective than placebos in aborting a cold; in frequent instances, claims made in behalf of placebos as an alleged aborter

of colds revealed the placebos to be more effective than the antihistaminic drugs. There is no validity to the contention that antihistaminic drugs are more effective if taken within a short time after the start of the common cold. A high percentage of side-effects occurred following ingestion of antihistaminic drugs.

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BOOK REVIEWS AND NOTICES

THE PATHOLOGY OF ARTICULAR AND SPINAL DISEASES. By DOUGLAS H. COLLINS, O.B.E., M.D., (Liverp.), Rheumatism Res. Fellow, Univ. of Leeds. Pp. 331; 199 ills. Balt.: Williams & Wilkins, 1950. Price, $7.00.

IN this excellent summary of the pathology of joint disease the Author has provided an atlas of pathological appearances not available in any other book. The format of the book is splendid and the illustrations themselves are unexcelled, both in the choice of specimens and the preparation of the cuts. While one may quibble in disagreeing with the ideas set forth in parts of the text, the general content is well presented and concise. This splendid presentation should be included in the library of pathologists, radiologists, orthopedic surgeons and rheumatologists. J. H.

PROCTOLOGY IN GENERAL PRACTICE. By J. PEERMAN NESSELRODT, M.S., M.D., Assoc. in Surg., Northwestern Univ. Med. School. Pp. 276; 64 ills. Phila.: W. B. Saunders, 1950. Price, $6.00.

THIS little monograph was dedicated to the late Collier Ford Martin, formerly Vice Dean and Professor of Proctology in the Graduate School of Medicine, University of Pennsylvania. The Author is an active proctologist. The volume, a practical treatise on the subject of proctology, is written primarily for the general practitioner and house officers. There are 15 chapters dealing with every aspect of anorectal disease. The illustrations are good, in fact very good. The book should prove to be exceedingly useful, and those who work in this field can learn much from reading it. The discussion of clinical proctology is excellent. I. R.

CLINICAL NUTRITION. Edited by NORMAN JOLLIFFE, M.D., F. F. TISDALL, M.D., and PAUL R. CANNON, M.D. For the Food and Nutrition Board of the National Research Council. Pp. 925; 12 ills., 61 in color. New York: P. B. Hoeber, 1950. Price, $12.00.

THIS remarkable volume by 3 outstanding investigators is a welcome addition to this important field. It is now agreed that nutrition is important in the prevention of illness and in the therapy of a wide variety of disorders. In this volume nutrition is discussed in its broadest aspects, from the standpoint both of the primary foodstuffs and of mineral metabolism.

The book is divided into 3 parts: 1) Diagnosis of Nutritional Deficiency; 2) The Nutrient Elements; and 3) Therapy and Prevention. The illustrations are remarkably well done. To prevent repetition, a number of these have been assembled in the appendix, where a wide variety of dietary patterns is also to be found. Every effort has been made to include that which is clinically significant or may become so in the near future and to omit material that is purely of academic interest. One might question the adequacy of the bibliographies, but this is a minor point for those who have to read in a single volume the major collection of clinical nutrition today. I. R.

PROGRESS IN CLINICAL ENDOCRINOLOGY. Edited by SAMUEL SOSKIN, M.D., Michael Reese Hosp., Chicago. Pp. 641; illustrated. New York: Grune & Stratton, 1950. Price, $10.00.

THIS monograph should be of value to all those interested in the rapidly progressing fields of clinical endocrinology. It is composed of 77 articles, the majority of which are succinct, well ordered summaries of known facts and current opinions concerning many clinically important phases of endocrinology. The Editor and the 90 other contributors are to be congratulated on the choice of subjects and the general level of excellence of the articles. Most of the contributors are well known investigators of the subjects about which they write. Many of the bibliographies contain references to important publications appearing in the first half of 1949. Careful consideration is usually given to the many factors apparently involved in the unsolved problems discussed. However, in a few instances the tone of the discussion is that of controversy rather than detached judgment. F. D.

LIVER INJURY. Trans. of the 8th Conference, April 28 and 29, 1949. Edited by F. W. HOFFBAUER, M.D., Pp. 164; 44 ills. New York: Josiah Macy, Jr. Foundation, 1950. Price, $1.60.

FOR some years past the Josiah Macy, Jr. Foundation has brought together for a series of 2 day annual conferences a small group of

investigators representing so far as possible all the branches of science that bear on a chosen problem, as for example liver injury. These conferences are informal, lively and stimulating round-table discussions later shared with a wider group in published transactions.

The present conference deals with the liver lobule (Knisely), the function of the hepatic artery (Markowitz), massive liver necrosis (György, Schwarz), the role of the liver and kidney in circulatory homeostasis (Shorr), metabolic behavior of the eviscerate rat (Ingle), liver glycogen and the protection of liver cells (Bollman), and locus of the beginning of dietary cirrhosis (Hartcroft). To each of these presentations is added a transcript of the discussion in which the various participants freely expressed their views. The Macy Foundation is to be congratulated on the continued success of the conferences.

B. L.

An Introduction to the Study of Experimental Medicine. By Claude Bernard. Translated by Henry Copley Greene. 2d printing. Pp. 226. New York: Henry Shuman, 1949. Price, $3.00.

As a pioneer in experimental medicine, Claude Bernard made explicit what many physicians of today vaguely accept without question. This Reviewer, almost a century later, knows of no clearer exposition of the essence of biological proof. The work is divided into 3 parts: Experimental Reasoning, Experimentation with Living Beings, and Applications of the Experimental Method to the Study of Vital Phenomena. C. B.

Lipidoses. Diseases of the Cellular Lipid Metabolism. By Siegfried J. Thannhauser, M.D., Ph.D., Assoc. Prof. of Med., Tufts College. Edited by Henry A. Christian, M.D. 2d ed. Pp. 224; 125 ills. New York: Oxford University Press, 1950. Price, $12.00.

This 2d edition of the reprint of Thannhauser's section in Oxford Loose-Leaf Medicine represents a tangible result of the Author's long-time interest in this subject. This veritable storehouse of information on diseases of cellular lipid metabolism has been brought up to date, although the concepts of the pathogenesis of the different lipidoses have not been basically changed. Among the alterations are the separation of xanthomatous biliary cirrhosis from the syndrome of essential xanthomatoses of the hypercholesteremic type; broadening of the discussion on idiopathic hyperlipemia and the classification of the Hand-Schüller-Christian syndrome as eosinophilic xanthomatous granuloma. The reëvaluation of this syndrome in the light of recent histologic data forms, for the Reviewer, one of the most interesting developments in the lipid field, although much that is repetitious in the write-up could be consolidated. A section of Niemann-Pick's disease in adults has been added. The basic chemical and physiologic portions have been expanded. Aside from a little over-emphasis in some places and under-emphasis in others, this volume is a masterful presentation of a confused and confusing subject. H. B.

Cell Growth and Cell Function. By Torbjoern O. Caspersson, M.D. Pp. 185; 94 ills. New York: W. W. Norton, 1950. Price, $5.00.

This book is based upon a series of lectures sponsored by the Salmon Committee of the New York Academy of Medicine. It consists of a report on the quantitative cytochemical studies carried out at the Karolinska Institute in Sweden by the Author and his associates during the past 15 years. The methods of microspectrophotometry of organic material are clearly described and the limitations as well as the advantages of the systems are objectively presented.

After an introduction and a chapter of general technical discussion, 5 chapters are devoted to various aspects of protein metabolism (nucleotides, metabolism during mitosis, cytoplasmic proteins, and protein metabolism in yeast, bacteria and viruses). The book closes with a short summarizing survey and a useful bibliography.

The material is well presented, quite readable and of interest to all investigators dealing with the metabolic processes of biological material. The Salmon Committee is to be complimented upon its selection of this work for publication in book form. D. C.

Thomas W. Salmon, Psychiatrist. By Earl D. Bond, M.D., with Paul O. Komora. Pp. 237; 1 ill. New York: W. W. Norton, 1950. Price, $3.00.

This book presents in a very readable form the life-work of an outstanding and greatly beloved psychiatrist. It tells of Dr. Salmon's pioneer work in the first quarter of this century in the field of mental hygiene, of his bringing about improved conditions in institutions for the insane and feeble-minded, and his constructive influence in the teaching of psychiatry in medical schools. It is an inspiring book about a man who had a strong influence upon American psychiatry.

W. P.

PROCEEDINGS OF THE FIRST CLINICAL ACTH CONFERENCE. Edited by JOHN R. MOTE, M.D., Med. Director, Armour Laboratories, with 178 Contributors. Pp. 624; 414 ills. Phila.: Blakiston, 1950. Price, $5.50.

THIS book, of 52 chapters, encompassing a wide range of the physiologic, metabolic and clinical aspects of ACTH, is a factual report of the projects in progress during the past 3 years, many of which have not been heretofore reported. It is stressed that the data are largely of a preliminary and tentative nature. The effects of ACTH in healthy human beings and in patients with various endocrinopathies and other disease syndromes are well documented and clearly presented. Among the side reactions are acne, moon face, pigmentation, edema, buffalo hump, hirsutism, electrolyte imbalance, mental disorders, hypertension, inhibition of menstruation and anaphylactoid reaction. Of special interest are the data on ACTH as a test of adrenal cortical integrity. The Authors amply verify that adrenal cortical function is involved in a large variety of diseases. Although no cures are claimed, some conditions appear to be favorably affected by ACTH. This is particularly true of the collagen "group", lymphomatous diseases, delirium tremens, and a few of the hypersensitivities. The mechanism of these beneficial effects are not presently understood although clarification may come from continued study of the pharmacodynamics of ACTH and the adrenal cortical steroids. Dr. Mote and the Armour Laboratories are to be commended for making available urgently awaited information so soon after presentation. The omission of an index is unfortunate. J. R.

THE NOSE. By THOMAS H. HOLMES, M.D., HELEN GOODELL, B.S., STEWART WOLF, M.D., and HAROLD G. WOLFF, M.D., Cornell Univ. Med. Coll. Pp. 172; 35 ills., 5 in color. Springfield, Ill.: Charles C Thomas, 1950. Price, $4.50.

THIS monograph is an interesting record of an experimental study of disturbances in nasal and respiratory physiology occurring in response to a variety of situational threats. An attempt has been made to correlate nasal dysfunction and nasal disease with problems of personality adjustment and noxious events; in short, to study man and his nose as a unit. For the reader who desires to maintain a balanced perspective, it would be well to bear in mind the following excerpt from the last paragraph: "It is not implied that all nasal disease stems directly from situations involving difficulties in interpersonal and social adjustments. There are other factors which set in motion the chain of events described." N. F.

THE CHEMISTRY OF INDUSTRIAL TOXICOLOGY. By HERVEY B. ELKINS, Ph.D., Chief of Lab., Mass. Dept. of Labor and Industry. Pp. 406; 22 ills. New York: John Wiley, 1950. Price, $5.50.

DR. ELKINS states that he "treats industrial poisons from the point of view of the chemist and engineer." He sticks to his promise, and his book deals with industrial processes and things which result from them rather than with symptomatology, pathology, and physiology. It is arranged intelligently and logically. The subject index is good; there is no author index, but there is a bibliography of 366 references arranged in the order in which they come in the text. Descriptions of methods, analytical procedures, concentrations of toxic solvents and various industrial poisons are given conventionally, clearly and fully.

The most valuable feature of this book is the fact that it is largely a careful account of the unusual practical problems that have been handled by Elkins and his laboratory in the Division of Occupational Hygiene of Massachusetts. These are the things that one wants from such a book. P. D.

PRACTICAL STATISTICS IN HEALTH AND MEDICAL WORK. By RUTH RICE PUFFER, Dr. P. H., Vanderbilt Univ. Pp. 238; 18 figs. New York: McGraw-Hill, 1950. Price, $3.75.

THERE is an increasing but often hazy appreciation of the importance of statistical methods in the fields of public health and of medicine; but, unfortunately, all too many of those concerned with the practical aspects of these professions have but little training in the use of statistics and need information on what data are required, on how to obtain them, on how to arrange them and analyze them. This book gives some of the general principles, and many illustrations from the public health programs in Tennessee. It has chapters on the value and uses of statistical data, on the methods of handling such data, on the presentation of data, on the method of study of development of disease during a period of time, and on the study of illness in populations. The book is clearly written and should prove useful to physicians and public health officers who by necessity or choice wish to employ statistical methods. B. L.

THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE. By CHARLES HERBERT BEST, M.D., and NORMAN BURKE TAYLOR, M.D. 5th ed. Pp. 1330; 601 ills. Balt.: Williams & Wilkins, 1950. Price, $11.00.

THIS new edition represents a successful attempt to add to an already large text the accounts of the many recent developments in physiological research. In spite of the space left by remissions and revisions, the book has grown considerably by the addition of new information and illustrations. The fundamental structure of the previous edition is maintained, but most of the sections are revised and brought to date. Notable changes have been made in subject matter of sections on blood, kidney function, metabolism, and vision. This text now stands even higher as an invaluable teaching aid and reference source. I. Z.

MEDICAL MANAGEMENT OF GASTRO-INTESTINAL DISORDERS. By GARNETT CHENEY, M.D., Clin. Prof. of Med., Stanford Univ. Pp. 456; 29 ills. Chicago: Year Book Publishers, 1950. Price, $6.75.

THE Author reviews the subject as it is met by the general practitioner, utilizing the approach of analysis by symptoms rather than the customary didactic discussion of disease entities. In the first 70 pages physical examination and the fundamental laboratory tests and special studies peculiar to the field are briefly discussed. The book contains many specific recommendations on symptomatic management, and in other ways reflects the wide practical experience of the Author. It is not intended to be a reference volume for the specialist, but rather an aid to the general practitioner in his daily practice. As such it will be found helpful. T. R.

ESSENTIAL UROLOGY. By FLETCHER H. COLBY, M.D., Ass't Clinical Prof. of Genito-Urinary Surgery, Harvard Medical School. Pp. 580; 342 ills. Balt.: Williams & Wilkins, 1950. Price, $8.00.

THIS new book is indeed aptly titled, for it contains all the "essentials" for making it an excellent textbook. Basic information concerning the genito-urinary organs is thoroughly covered without redundancy. Part I consists of 11 chapters dealing with embryology, anatomy and physiology; Part II of instructions for the examination of the patient; and Part III discusses diseases of the genito-urinary organs. Basic principles of treatment are emphasized. The entire book is well and concisely written. It is highly recommended. B. H.

SECRETORY MECHANISM OF THE DIGESTIVE GLANDS. By B. P. BABKIN, M.D., Formerly Prof. of Physiology, McGill, Odessa, Russia, and Dalhousie Universities. 2d ed. Pp. 1027; 233 ills. New York: P. B. Hoeber, 1950. Price, $20.00.

THIS book is a classical and modern treatise covering the anatomy, histology and physiology of the digestive glands. Drawing upon his immense experience, the Author analyzes the crucial experiments necessary for intelligent interpretation of the problems in this field. He is always careful to present the data on all sides of controversial questions, and at the same time gives the Reader his own considered interpretation and integration of the varying results. Thus the book may be used, not only as a text for the study of the digestive glands but also as a source for basic references. The latter function is facilitated by a comprehensive and well-organized author and subject index. The book is at its best on the gastric and salivary glands, but also has detailed information about the pancreas, the glands of the small and large bowel, and the roles of the nervous system and acetylcholine in the function and dysfunction of these structures. S. M.

GASTROSCOPY. THE ENDOSCOPIC STUDY OF GASTRIC PATHOLOGY. By RUDOLF SCHINDLER, M.D., 2d ed. Pp. 458; 366 ills., 120 color plates. Chicago: Univ. Press, 1950. Price, $20.00.

THIS is a well-organized and beautifully illustrated encyclopedia of gastroscopy. The father of modern gastroscopy gives a clear discussion of the history of this procedure and describes the anatomical relationships important to the gastroscopist. The main portions of the book emphasize the proper techniques and pitfalls in gastroscopy, and the proficiencies and deficiencies of the gastroscopic method in the diagnosis of various lesions and malformations of the stomach. The controversial subject of gastritis is not discussed as completely as is done in Schindler's book devoted entirely to gastritis. S. M.

UROLOGICAL ASPECTS OF SPINAL CORD INJURIES. By GEORGE C. PRATHER, M.D., Harvard Medical School. Pp. 146; 38 ills. Springfield, Ill.: Charles C Thomas, 1949. Price, $3.75.

THIS book presents concisely the normal anatomy and physiology of the urinary bladder. From his large experience in caring for paraplegics in Army hospitals, the Author

has clearly described urinary tract complications due to spinal cord injury and has reviewed the necessary steps to re-establish vesical function. The book should be particularly useful to neurological and neurosurgical resident physicians who see and care for many cases of spinal cord injury with associated urinary tract complications.

B. H.

CHEMICAL DEVELOPMENTS IN THYROIDOLOGY. By WILLIAM T. SALTER, Prof. of Pharmacology, Yale Univ. Pp. 87. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

THIS small monograph presents the recent advances in our knowledge of the thyroid. This is done under the headings: Synthesis of the Thyroid Hormone, The Blocking of Thyroid Activity, Circulating Thyroid Hormone, and The Application of Radio-iodine. Dr. Salter is not only an authority on the thyroid but also a master of the art of medical writing. The result is one of the best short monographs that has appeared in recent years.

F. L.

DISEASES OF CHILDREN. Vol. 2. Edited by DONALD PATERSON, M.D. (Edin.), and ALAN MONCRIEFF, M.D. (Lond.). 4th ed. Pp. 1033; illustrated. Balt.: Williams & Wilkins, 1949. Price, $10.00.

THIS complete revision of a standard British textbook of pediatrics is now brought out in 2 parts, Volume 1 having been published in 1947. The current edition contains much new material, by 24 contributors, and a good collection of illustrations. Its chief appeal to American readers will rest in its excellent practical descriptions of symptomatology and clinical signs. The paragraphs on therapy do not discuss many of the chemotherapeutic agents found in our neighborhood drug stores.

I. W.

THE ABNORMAL PNEUMOENCEPHALOGRAM. By LEO M. DAVIDOFF, M.D., Clin. Prof. of Neurosurgery, New York Univ., and BERNARD S. EPSTEIN, M.D., Instr. in Clin. Radiology, Long Island Coll. of Med. Pp. 506; 659 ills. Phila.: Lea & Febiger, 1950. Price, $15.00.

THE Authors are to be congratulated on the excellence of this new book. It should be stated in the beginning of this review that this publication does not in any way take the place of a previous volume, "The Normal Encephalogram" by Davidoff and Dyke.

Dr. Dyke, I am sure, would be delighted that this magnificent volume has been dedicated to him. The Authors have covered the subject thoroughly; nothing has been left out; at least the Reviewer has not discovered any important omission. The Authors have put together a world of information which is encyclopedic in nature. They have covered a tremendous amount of literature, and must have consulted a major portion of the work on this subject. Although they have not considered the subject of arterial encephalography, it is quite possible that this procedure is to be the subject of an additional volume.

One might suggest that in any subsequent volumes a greater effort be made to improve the illustrations. In some of them, one cannot see the air shadows described in the legend. It is realized that many of these shadows are difficult to reproduce in a book except on an extra fine-caliber paper. The Reviewer also feels that the large arrows and large letters detract from the appearance of the illustrations. The work is so well done, however, and complements in so satisfactory a manner the work found in "The Normal Encephalogram", that the Reviewer hesitates to say anything in the way of criticism.

The publishers have prepared this work satisfactorily. The quality of the paper is adequate for reading and, as stated above, most of the illustrations are good, though a few fail to show some of the air shadows that would be most helpful if they could be seen.

E. P.

ELECTROCARDIOGRAPHY. FUNDAMENTALS AND CLINICAL APPLICATION. By LOUIS WOLFF, M.D., Assoc. in Medicine, Harvard. Pp. 187; 110 ills. Phila.: W. B. Saunders, 1950. Price, $4.50.

CARDIOGRAPHY. By WILLIAM EVANS, M.D., London Hospital. Pp. 140; 211 ills. St. Louis: C. V. Mosby, 1950. Price, $6.75.

A MANUAL OF CARDIOLOGY. By THOMAS J. DRY, Assoc. Prof. of Med., Univ. of Minnesota. 2d ed. Pp. 355; 97 ills. Phila.: W. B. Saunders, 1950. Price, $5.00.

THESE 3 books are addressed to the medical student and to the general practitioner.

Wolf's book is divided in 2 parts: The Basic Principles of Electrocardiography and The Clinical Applications. The basic principles are essentially those of the dipolar theory of electrocardiography as developed primarily by Wilson and his school. The Author succeeds admirably in accomplishing his task clearly and concisely, and for this reason his book is recommended to those for whom it was written. Caveat emptor! The title is a misnomer. Not only is a discussion of the arrhythmias omitted, but also the effects of drugs, particularly digitalis, of infections,

metabolic disturbances, and even the effects of chronic coronary artery disease. The Reviewer thinks that the Author unduly minimizes the importance of quantitative measurements in the diagnosis of the abnormal electrocardiogram. He also believes that any student interested in basic principles should be interested in the validity of these principles. Hence he regards the omission of a selected bibliography as a mistake.

Evans' book is likewise divided into 2 parts: Electrocardiography and Phonocardiography. He uses the empirical approach to electrocardiography. No attempt is made to discuss principles. No mention is made of V leads, which are now regarded as mandatory by the British Heart Journal. Indeed, on page 1, the left arm electrode of Lead 3 is called an indifferent electrode! The key to electrocardiographic interpretation frequently gives a clinical diagnosis rather than an electrocardiographic interpretation. The section on phonocardiography represents Evans' personal observations. His conclusions have recently been seriously questioned on the basis of inadequacy of his phonocardiographic apparatus. Until this whole problem is settled, this material does not appear proper for an elementary didactic book.

For all these reasons, the book is not recommended to the American student and practitioner.

Dry's book is the 2d edition of a manual first published in 1943. For its size, it contains an amazing store of information all of which is given clearly, accurately and tersely. It is highly recommended to students and to all physicians in general practice. It will also be of value to specialists in internal medicine whose prime interest is not in cardiology.

L. S.

Regional Dermatologic Diagnosis. By Erwin Epstein, M.D., Oakland (Cal.) Veterans Hosp. Pp. 328; 148 ills. Phila.: Lea & Febiger, 1950. Price, $6.00.

Epstein has introduced a new note in dermatologic texts for the practitioner. Instead of the usual presentation of diseases grouped on the basis of morphology or on probable etiologic background, he employs a system based on a single easily recognized characteristic, namely, location. This points up at once the factors involved in establishing an early and correct diagnosis. While one might look upon this procedure as an artificial non-dynamic device for aiding the physician confronted with a dermatologic problem, it has the advantage of being practical.

The volume has 31 chapters, each dealing with a single area and divided into sections, under each of which dermatoses are arranged and described in the order in which they are most likely to be met. The text material contains a moderately full description of the processes as well as some suggestions for study and therapy. At the end of each chapter there is a table listing the more important processes and the more important features of each. These generally excellent tables are unfortunately set up in type which is too small for comfortable reading.

The book is well constructed, the illustrations well chosen, and there are relatively few typographical errors. The viewpoints expressed are generally acceptable. The Author on the whole has attained his objective.

H. B.

Medical Clinics of North America. New York Number. Symposium on Cardiovascular Diseases. Pp. 609-937. Phila.: W. B. Saunders, May 1950. Price, $15.00 a year.

For those aware of the difficulty of keeping up with recent advances in cardiovascular knowledge and techniques, such a review as this is invaluable. To get such material otherwise would entail considerable time spent in reviewing numerous periodicals, since much of the information is too new for appearance in standard texts.

H. Z.

Genealogy of Gynaecology. By James V. Ricci, M.D., Clinical Prof. of Gynaecology and Obstetrics, N. Y. Med. Coll. 2d ed. Pp. 494. Phila.: Blakiston, 1950. Price, $8.50.

The 1st edition of this interesting book was reviewed in this Journal (**208**, 277, 1944). The present edition, enlarged and thoroughly revised by Curt Proskauer, avoids most of the shortcomings noted in the 1st; and the biggest lack—the story's ending with the 18th century—has been met by the Author with the publication in 1946 of "One Hundred Years of Gynecology (1800-1900)". Internal evidence indicates that the undated Preface was prepared for this 2d edition. The undated Introduction, on the other hand, appears to be that of the 1st, as it states that the 1800 to 1900 period "will be covered by a subsequent volume".

A review of the Author's most recent book in this field, "The Development of Gynecological Surgery and Instruments", appeared in this Journal's June, 1950, number. This trilogy offers one of the most complete coverages in English of the history of a medical specialty.

E. K.

THE PHYSIOLOGY OF TISSUES AND ORGANS. By DOUGLAS H. K. LEE, M.D., Prof. of Physiological Climatology, Johns Hopkins. Pp. 159; 30 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $4.00.

DESIGNED to be an introduction to a course in medical school physiology, this small book is divided into 2 parts. Part 1 deals with general principles of chemistry and their application to cellular physiology. Various cell types are considered in short chapters. The function of these cells when organized in tissues and organs is studied in Part 2.

The Author has succeeded in presenting a well written and concise but thorough introduction to mammalian physiology. W. L.

TEXTBOOK OF ENDOCRINOLOGY. Edited by ROBERT H. WILLIAMS, M.D., Prof. of Medicine, Univ. of Washington Medical School, Seattle. Pp. 793; 168 figs. Phila.: W. B. Saunders, 1950. Price, $10.00.

THIS is an excellent textbook. The contributors are outstanding clinical investigators of the fields about which they write. Every effort is made by the Authors to correlate the physiological and anatomical data with the clinical aspects of endocrine disturbances. There are 7 chapters dealing with disturbances of various glands. The other 5 discuss the general principles of endocrinology, growth and development, the neuroendocrine and psychodynamic aspects of endocrinology, obesity, and laboratory procedures. This book is highly recommended not only to students and physicians in general, but to those specializing in this field.

F. D.

NEW BOOKS

Homöotherapie. Von Dr. KARL STAUFFER. Pp. 678. Stuttgart, Germany: Marquardt & Cie., 1950. Price D.M. 35.

A Histology of the Body Tissues. By MARGARET GILLISON, Univ. of London. Pp. 220; 103 ills. Balt.: Williams & Wilkins, 1950. Price, $3.50.

Sigm. Freud. Aus den Anfängen der Psychoanalyse. Briefe an WILHELM FLIESS. Pp. 477. London: Imago, 1950. Price, 30 s.

Light Therapy. By RICHARD KOVACS, M.D., New York Polyclinic Med. School and Hospital. American Lecture Series No. 57. Pp. 112; 28 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.25.

Personality in Peptic Ulcer. By A. J. SULLIVAN, M.D., and T. E. MCKELL, M.D., Ochsner Clinic, New Orleans. Pp. 112; 13 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $3.00.

Antimetabolites. By D. W. WOOLLEY, *et al.* Annals N. Y. Acad. Sci., 52, 1197-1378. New York: The Academy, 1950. Price, $2.75.

Allgemeine Konstitutionslehre. Von Dr. Phil. et Med. K. SALLER, Univ. München. Pp. 210. Stuttgart, Germany: Marquardt & Cie., 1950. Price, 160 S., Ln.DM 9.50.

Jugendpsychologie. Von Prof. Dr. Med. ERICH STERN. Vol. 4. Pp. 164. Stuttgart, Germany: Marquardt & Cie., 1950. Price, 224 S., Ln.DM 12.50.

The Physiological Basis for Oxygen Therapy. By JULIUS H. COMROE, JR., M.D., Prof. of Physiology and Pharmacology, and ROBERT D. DRIPPS, M.D., Prof. of Anesthesiology, Univ. of Penna. American Lect. Ser. 42. Pp. 85. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

Types of Diabetes Mellitus and Their Treatment. By ARTHUR R. COLWELL, M.D., Assoc. Prof. of Medicine, Northwestern Univ. American Lect. Ser. 67. Pp. 97. Springfield, Ill.: Charles C Thomas, 1950. Price $2.25.

Enzymes, Growth and Cancer. By VAN R. POTTER, PH.D., Prof. of Oncology, Univ. of Wisconsin. American Lect. Ser. 75. Pp. 64. Springfield, Ill.: Charles C Thomas, 1950. Price, $1.85.

NEW EDITIONS

ELEMENTS OF MEDICAL MYCOLOGY. By JACOB HYAMS SWARTZ, M.D., Ass't Prof. of Dermatology, Harvard Medical School, with ETHEL M. ROCKWOOD, M.D. Introduction by FRED D. WEIDMAN, M.D. 2d ed. Pp. 240; 140 ills. New York: Grune & Stratton, 1950. Price, $5.50.

THE book is very much like the previous edition (reviewed in this Journal, **207**, 277, 1944), except that a little new material has been incorporated. Paragraphs on the coccidioidin and blastomycin tests, penicillin, streptomycin, and gliotoxin are the main additions. H. M.

TEXTBOOK OF ABNORMAL PSYCHOLOGY. By CARNEY LANDIS, Prof. of Psychology, Columbia Univ., and M. MARJORIE BOLLES. 2d ed. Pp. 634. New York: Macmillan, 1950. Price, $5.00.

THE MASK OF SANITY. By HERVEY CLECKLEY, M.D., Prof. of Psychiatry and Neurology, Univ. of Georgia. 2d ed. Pp. 569 St. Louis: C. V. Mosby, 1950. Price, $6.50.